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Access to medicines for multiple sclerosis: Challenges and opportunities

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Executive Summary

Multiple sclerosis (MS) is a disorder of the central nervous system (brain and spinal cord) affecting over 500,000 Europeans. It affects three times as many women as men, with the diagnosis typically occurring in patients aged in their 20s or 30s and is more prevalent in Northern Europe (as well as North America, Australia and New Zealand). The symptoms vary from patient to patient but include fatigue, vision problems, difficulties walking or speaking, memory problems and depression. It can lead to severe and permanent disability. The symptoms often appear periodically – known as relapses – which may last for a few hours, or many months. Although the causes of MS remain unknown and there is currently no cure, over the last twenty years a number of treatments have been developed that reduce the number of relapses and slow the progression of the disease. Biogen Idec asked Charles River Associates (CRA) to examine how access to innovative treatments for multiple sclerosis (MS) varies across European countries, the factors explaining this and the policy lessons that can be drawn.

Access to Disease Modifying Drugs (DMD)

There have been a number of studies of access to MS treatments in Europe. The most well-known of these is Kobelt and Kasteng (2009). This looked at available evidence on prevalence, the costs to society and difference in access across European countries and discussed the determinants of patient access. They found that there was a wide variation across European member states in 2008.

In order to estimate patient access to treatment, we calculated the proportion of the MS patient population receiving treatment using the absolute number from 2013 and the total population with MS in 2013. According to our analysis using updated prevalence data and updated calculation on the number of patients receiving treatment, we find that although there has been a catch up from poor performers such as the UK and Eastern European countries (e.g. Romania, Czech Rep), the best performers have also increased. The result of this is that whereas Kobelt found a range of 6% to 58% for the set of countries, we find a range from 13% to 69% as illustrated in Figure 1. This shows that significant inequalities in access still remain even in Western European countries with access to treatment as high as 69% in Germany and only around 21% in the UK compared to 13% in Poland.

Figure 1: Proportion of total MS patient population receiving DMDs in selected European countries (2013)
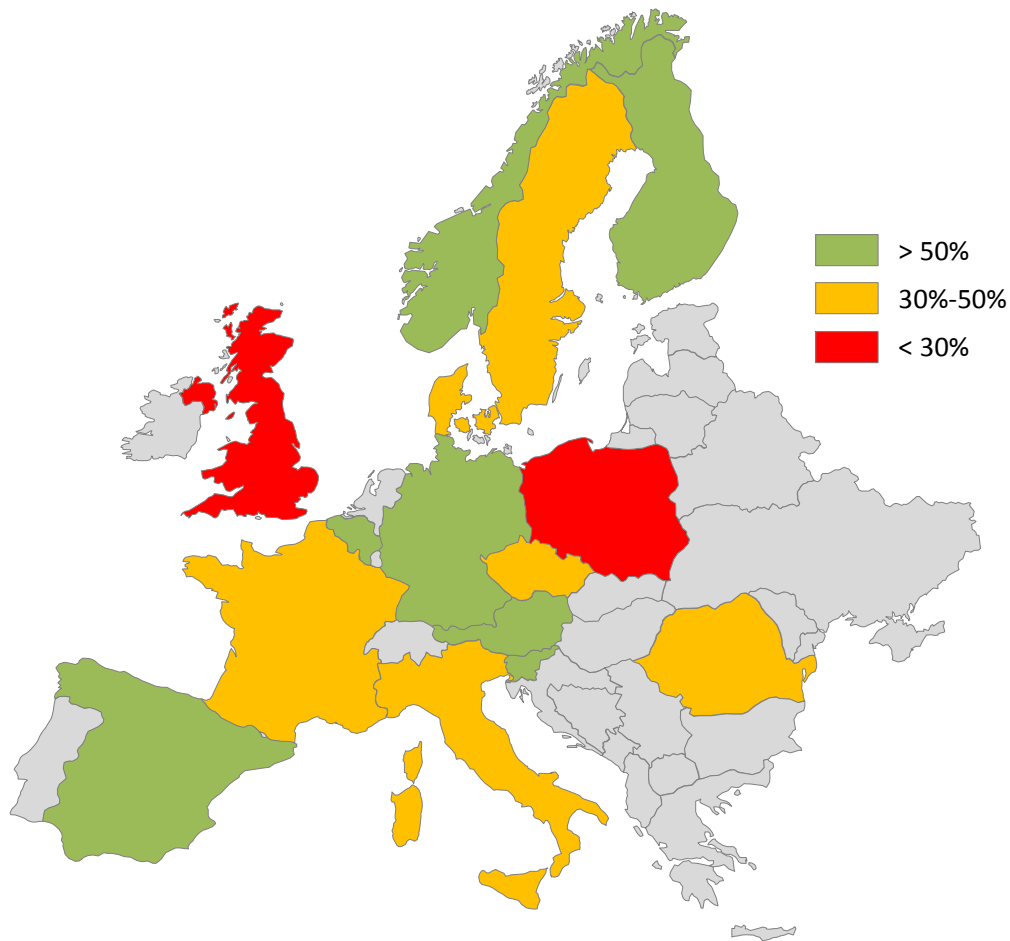
Source: *CRA analysis using IMS 2013, local MS societies, MS atlas 2013, GERS (France), Farmastat (Norway)*

However, it is important to note that the calculation of access depends critically on the definition being used. As only patients with Relapsing-remitting MS (RRMS) and Secondary-progressive MS (SPMS) are eligible for DMDs, a better measure of access would account for the types of patient. In some countries, studies exist that have looked at the level of access for different sub-populations.[1] RRMS patients generally have much better access to DMDs than other patients sub-groups (i.e. SPMS) with access ranging from 59% in the UK to 75% in Sweden and 91% in France.

This shows that we need to measure access with considerable care. Indeed, in Sweden there is a target of treating 75% of patients with RRMS, suggesting that high levels of access are being achieved.

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[1] Karampampa, K., Gustavsson, A., Miltenburger, C., & Eckert, B. (2012). Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. Multiple Sclerosis Journal, 18(2 suppl), 7-15.

Another picture emerges if we look at the composition of the products being used. There are significant differences between European countries in terms of access to innovative treatments when we compare existing first line treatments to more recent second line treatments (Natalizumab & Fingolimod)[2]. Scandinavian countries provide better access to innovative second line treatments in Europe (Norway 39%, Sweden 31.8%, Denmark 29.5% of products are second line treatment) followed by France, Austria and Belgium (ca 20%) were as Eastern European countries have significantly lower proportions (Poland and Romania around 3-4%).

Determinants of access

There are a variety of potential explanatory factors that might have an influence over the reimbursement and prescription of innovative treatments for MS patients and could potentially vary across countries. These include:

- Diagnosis and clinical management of MS.

- Differences in the reimbursement process and patient eligibility for treatment.

- The affordability of MS drugs.

- The use of patient registries or databases.

Diagnosis and clinical management of MS

There is a correlation between the level of access and the healthcare infrastructure (as proxied by the number of neurologists). Access to a neurologist is seen as particularly problematic in some member states. For example, in the UK (which continues to have low levels of access), the number of neurology consultants specialised in MS has risen from 1 per 200,000 people in 1998 to 1 per 100,000 in 2013 but remains substantially lower than in other European member states.

More broadly, there is also considerable variation in specialised neurology and neurological rehabilitation services. Neurologists are not the only healthcare professionals that can assist in providing access to MS treatment. There are a number of studies that have highlighted the role that nurses play in identifying MS symptoms and the management of any adverse events of treatment. In addition to assisting in the management of the disease, nurses are also important as they encourage the use of new treatments.

We have also reviewed the clinical guidelines that have been used in different European member states. Although there are differences in clinical guidelines, these do not seem to explain much of the variation. There are, however some countries (such as the Czech Republic) with low access and restrictive guidelines where this appears an important barrier to access.

Differences in the reimbursement process and patient eligibility for treatment

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[2] Additional non DMD treatments such as Fampyra and Sativex are not included in this analyses as these drugs are to reduce symptoms which are taken in parallel to DMDs. These two products therefore do not account for additional patient numbers.

Although in most countries all first line products are reimbursed, there are restrictions imposed on the use of the medicines. These reimbursement restrictions could be another factor contributing to the following countries being amongst the four countries with the lowest access to MS DMDs – Poland at the bottom with 13%, and Romania and Czech Republic at 39%.

- In Romania, reimbursement to treatment for patients eligible for state-funded treatment is approved on a case-by-case basis according to whether funds are available. In 2013, 2,300 MS patients received state-funded DMDs, with 500 MS patients on the waiting list and approximately 200 new patients are approved to receive subsidised treatment each year. [3]

- In the Czech Republic, there has been no budget increase for hospitals for pharmaceuticals since 2010, resulting in a high number of untreated patients in the Czech Republic. Treatment waiting lists were also put in place in 2011.[4]

- In Poland, patients can be treated by a DMD only for a maximum of 5 years.[5] After 5 years, the treatment "spot" is transferred to the next person on the treatment waiting list.[6]

It seems reasonable to conclude that these restrictions are relevant factors in explaining the lack of access in CEE markets. In terms of Western European markets recent HTA decisions are relatively similar across countries. The biggest impact appears to be in the delays that these reimbursement restrictions cause to patient access.

The affordability of MS drugs

Another explanatory factor is the price of medicines. We would expect that countries with a higher income pay higher prices, but access could depend on the affordability of medicines (and associated medical costs). In terms of affordability, we do find a relationship between affordability and improved access. The affordability in CEE markets, in particular, appears to be a barrier to access. Although this has improved over the last five years, with a corresponding increase in access, affordability is still higher in western European markets and appears to continue to act as a barrier to access in CEE markets.

The need for patient registries or databases

MS registries and databases have been developed in a number of European member states. These are seen as key tools in disease management, allowing disease characteristics in

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[3]   Nine O'Clock (2013), "6000 to 8000 Romanians diagnosed with multiple sclerosis", available at http://www.nineoclock.ro/6000-to-8000-romanians-diagnosed-with-multiple-sclerosis/

[4]   Pospiskova, "Multiple sclerosis in Czech Republic"

[5]   EMSP, "Parliamentary event in Poland: 'The faces of MS'", available at http://www.emsp.org/news/emsp-member-news/213-parliamentary-event-in-poland-the-faces-of-ms, accessed January 7, 2014; Ministry of Health (2012), "Appendix B.29: Treatment of multiple sclerosis (ICD-10 G 35), available at http://www.ptsr.org.pl/pl/?poz=Top/B/B10/80

[6]   MS Ireland (2013), "Emma Talks at Polish MS Society event", available at http://www.ms-society.ie/blog-articles/1357-emma-invited-to-polish-ms-society

large populations to be studied and monitoring the long-term outcome of disease-modifying therapies. This helps provide information on the provision of treatments, services and supplies within a given area.

Policy implications

In order to reduce the variation in access there are a number of policy proposals worth considering:

- In some markets there is a relationship between access to medicines and the level of healthcare spending in diagnosis and treatment of MS. Addressing this requires greater investment in healthcare infrastructure devoted to treating and managing the disease. Given the increasing prevalence of MS, countries with low levels of access need to consider devoting more resources to MS, for example by increasing the number of neurologists and MS nurses.

- Political leadership through the development of a national strategy is essential to ensure consistency in the standard of care over time, to address the variations in service provision for people with MS and to provide a framework to increase access more rapidly. National registries, linked to an EU registry (EUreMS), need to be developed in order to measure the prevalence of MS country by country and to assess and enhance the status of people with MS. It is also important that clinical guidelines are kept up to date and more importantly that they are actually used in practice. The development of goals to achieve them will ensure an assessment is made regarding the appropriate level of coverage to aim for.

- Affordability is a key barrier to access for MS products. Some policies prevent prices from reflecting the level of income of each market, such as inappropriate international price benchmarking, where high income countries adjust their prices towards those in low income countries. These practices, as well as the promotion of product re-exportation into high income countries, which contribute to shortages in low income countries, should be reconsidered to improve affordability and patient access.

- To the extent that affordability can be improved, this would allow the removal of arbitrary administrative processes that are being used to manage budgets allowing greater access to patients on the basis of clinical judgement and bring significant benefits to the health system and even the economy.

1.   Introduction

Biogen Idec asked Charles River Associates (CRA) to examine how access to innovative treatments for multiple sclerosis (MS) varies across European countries and the policy lessons that can be drawn.

1.1.   Background and previous studies on variation in access to MS

MS is a disorder of the central nervous system (brain and spinal cord) affecting over 500,000 Europeans. It affects three times as many women as men, with the diagnosis typically occurring in patients aged in their 20s or 30s and is more prevalent in Northern Europe (as well as North America, Australia and New Zealand). The symptoms vary from patient to patient but include fatigue, vision problems, difficulties walking or speaking, memory problems and depression. MS can lead to severe and permanent disability. The symptoms appear periodically – relapses – which may last for a few hours, or many months. The causes of MS are unknown and there is currently no cure but over the last twenty years a number of treatments have been developed that modify the progression of the disease.

There have been a number of previous studies on how patient access to MS treatments varies between European countries. The most well-known report was undertaken by Kobelt and Kasteng in 2009 for the European Federation of Pharmaceutical Industries and Associations (EFPIA).[7] This looked at available evidence on prevalence, the costs to society and differences in access across European countries and discussed the determinants of patient access. They found that there was a wide variation: whereas in Western Europe around 44% of patients are on treatment, in Central and Eastern Europe (CEE) this percentage is between 6% and 42%. Even in the largest European countries, there were significant outliers with the UK having less than 10% of patients on treatment. In terms of explanation, they found that the large variations in patients with access to innovative drugs could be explained by economic differences among European economies. However, they found that price levels do not reflect the affordability levels in different markets. They also identified differences in medical practice, the ease of access to care and availability of care.

Since 2008 the European Multiple Sclerosis Platform has published the MS Barometer. This includes a comparison of access using data collected through an online questionnaire completed by MS patient organisations across Europe. Since 2008, this has been updated in three subsequent editions of the MS Barometer in 2009, 2011 and 2013.[8] This has shown that access continued to vary dramatically across Europe countries.

The aim of this paper is to update the Kobelt report, examine the extent that access to MS treatments has changed, particularly as a number of new MS treatments have been launched

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[7]   Kobelt and Kasteng (2009), "Access to innovative treatments in multiple sclerosis in Europe", a report prepared for the European Federation of Pharmaceutical Industry Associations (EFPIA). Available at: http://www.comparatorreports.se/Access%20to%20MS%20treatments%20-%20October%202009.pdf. We refer to this as the "Kobelt report".

[8]   Ibid.

and look more closely at the reason for variation in access and the corresponding policy implications.

1.2. Defining 'access'

Whilst there is currently no cure available for MS, there are interventions that can significantly reduce the impact the condition has on the lives of those with MS.[9] These range from traditional pharmacologic medicines to fatigue management courses and cognitive behavioural therapy which are available to target the symptoms or slow down the progress of the condition.

In order to measure the level of access, we estimate the number of patients who are being treated with disease modifying drugs (DMDs). DMDs reduce the number of relapses experienced by MS patients and potentially slow the rate of disability in the long term. There are currently seven DMDs licensed in Europe.[10] Symptomatic treatments have also been made available recently, however access to them is much more limited than with DMDs.[11] We discuss the use of symptomatic treatments but do not include them in our definition of access. These medicines are used in parallel with DMDs and therefore do not treat additional sets of patients.

To determine access, we need to consider the relevant population of patients who have MS. There are four categories within MS, only two of which qualify for treatment with DMDs. The four subcategories of MS are: [12] [13]

- Relapse remitting MS (RRMS): The majority of MS patients initially present with this form of the disease, characterised by clearly defined disease relapses with full recovery or with sequela and residual deficit upon recovery.

- Secondary progressive MS (SPMS): Some patients with RRMS will transition into this sub-form, characterised by disease progression with or without occasional relapses, minor remissions, and plateaus.

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[9] Avonex (beta interferon-1a), Rebif (beta interferon-1a), Betaferon (beta interferon-1b), Extavia (beta interferon-1b),, Copaxone (glatiramer acetate), Tysabri (natalizumab), Gilenya (fingolimod). Other treatments for relapses using steroids are also available as well individual symptom relief drugs but these are normally taken in parallel to DMDs.

[10] Bevan S, Zheltoukhova K, McGee R, Blazey L (2011), "Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis", The Work Foundation.

[11] For example, Fampyra was granted a marketing authorisation valid throughout the European Union by the European commission in 2011 to improve walking ability in adults with multiple sclerosis (MS) who have a walking disability. European Medical Agency (2011), "EPAR summary for the public - Fampyra", EMA.

[12] "Some elements on the situation of multiple sclerosis in the European Union" Directorate C - Public Health and Risk Assessment C2 - Health information.

[13] Kieseier, B. C., & Hartung, H. P. (2003, June). Current disease-modifying therapies in multiple sclerosis. In Seminars in neurology (Vol. 23, No. 02, pp. 133-146). Copyright© 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.:+ 1 (212) 584-4662.

- Primary progressive MS (PPMS): Approximately 10% of the MS population presents a disease progression from the onset with occasional plateaus and temporary improvements.

- Progressive relapsing MS (PRMS): The least common form is a progressive disease from onset with acute relapses, with or without full recovery, with periods between relapses characterised by continuous progression.

RRMS (ca. 60%) and SPMS (ca. 25%) correspond to the majority (ca. 85%) of the MS population.[14] [15] RRMS patients and SPMS patients with relapses (ca. 10-15% of SPMS patients) are the only two categories of MS patients that qualify for treatment with DMDs under European Medicines Agency (EMA) guidelines.[16] The EMA has recommended several beta-interferons, Glatimer acetate (Copaxone), as first line treatment of relapse remitting MS (RRMS). Natalizumab and Fingolimod can only be used as a second line treatment for RRMS. Only Betaferon and Extavia have been approved by the EMA for secondary progressive MS (SPMS) (see Figure 2). However, currently, none of these products are approved for primary progressive MS (PPMS) or progressive relapsing MS (PRMS).

In addition to the above treatments, the EMA has recently approved three new DMD treatments for MS, including Teriflunomide (Aubagio), Dimethyl Fumarate (Tecfidera) and Alemtuzumab (Lemtrada) which is administered via intravenous infusion.[17] However, we have excluded these three recently approved products from our analysis as no sales data was available at the time of our analysis. Also excluded were the symptomatic treatments which do not contribute directly to the calculation of additional patient numbers (Fampridine and Nabiximols).

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[14]   Karampampa, K., Gustavsson, A., Miltenburger, C., & Eckert, B. (2012). Treatment experience, burden and unmet needs (TRIBUNE) in MS study: results from five European countries. Multiple Sclerosis Journal, 18(2 suppl), 7-15.

[15]   Secondary progressive multiple sclerosis: current knowledge and future challenges. Marco Rovaris et al.. http://neurology.thelancet.com Vol 5 April 2006

[16]   EMA Summary of Product Characteristics, as accessed via the EMA website. In reality, all four groups of patients are treated with DMDs.

[17]   PharmaTimes (17 September 2013) Europe approves Sanofi MS drug Lemtrada; available at http://www.pharmatimes.com/article/13-09-17/Europe_approves_Sanofi_MS_drug_Lemtrada.aspx

Figure 2: **EMA indications for disease modifying therapies (DMDs) used in this analysis**
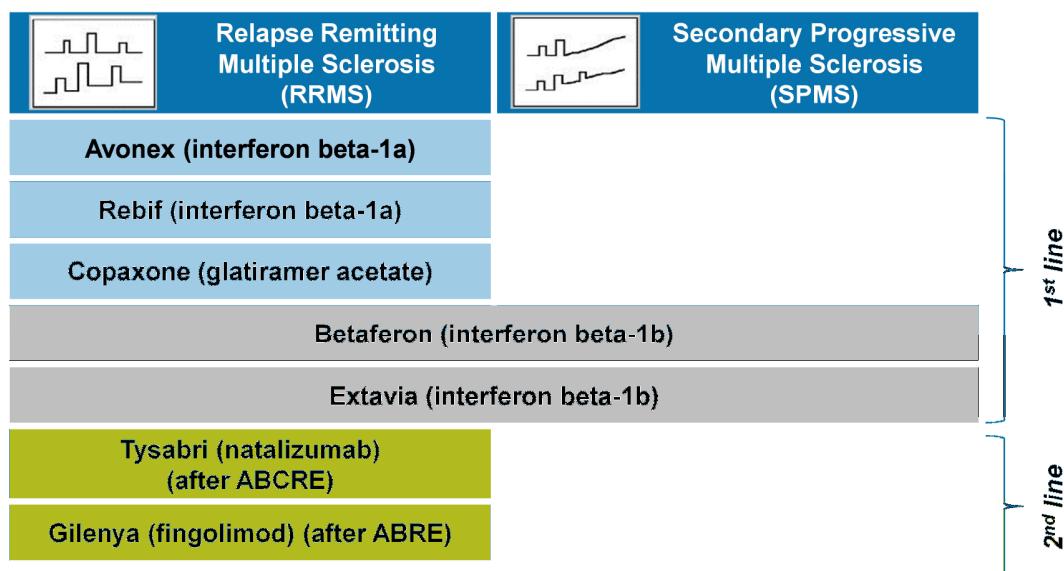
Source: CRA analysis based on EMA Summary of Product Characteristics, as accessed via the EMA website.

As there is no single source providing a standardised quantification of the different types of MS, we have followed the convention of Kobelt and measured access as the percentage of all MS patients who are being treated with DMDs.[18]

1.3.   Our approach

Whilst Kobelt et al relied entirely on IMS data[19] to calculate the number of patients with access to treatment we have taken a slightly different approach. IMS has some significant limitations for MS medicines (primarily because of the different supply chains used in different markets. Delivery direct to patient is used in some markets, whilst in others the hospital market is not covered reliably by IMS).[20] As there is no single readily available source on the number of patients treated in any country in Europe, we therefore focus on a smaller

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[18]   This is clearly a crude definition, as it does not take into account if the product is being used according to its label or whether the product is appropriate given the diagnosis of the patient. However, it does allow us to make cross-country comparisons and compare to the earlier studies. Where possible we discuss how the result would differ if we only allow from RRMS and SPMS patients.

[19]   IMS data is an industry standard data sources that captures data on the volume and value of sales by undertaking audits across international pharmaceutical markets.

[20]   This was recognised by Kobelt who made adjustments such as excluding countries with questionable data and making corrections to the calculation of the proportion of diagnosed patients on treatment at the end of 2008, and for the mean cost of biologics per patients. Kobelt and Kasteng (2009), "Access to innovative treatments in multiple sclerosis in Europe", a report prepared for the European Federation of Pharmaceutical Industry Associations (EFPIA).

selection of European countries where IMS is representative in order to be sure that the estimates of access are meaningful and have supplemented this with country specific data sources to ensure we have a wide range of different circumstances.

We also need prevalence data to calculate access. Again, there is no perfectly consistent data source on prevalence. However, compared to the situation in 2008, the availability and quality of data has significantly improved. Unlike Kobelt that derived prevalence estimates, we have primarily relied on data from the MS Atlas.[21]

The selection of the countries was based on two steps. In the first step, we chose countries which were included in the analysis by Kobelt and Kasteng (2009), where there is recent data on prevalence in MS Atlas and where the IMS data is seen as representative. Secondly, to ensure that we had a range of different country circumstances we supplemented this with alternative data sources.

The countries that passed the first steps are represented in dark green in Figure 3. Despite a covering a variety of countries in Northern, Southern, and Western Europe, there is no coverage of Eastern Europe.

Figure 3: Choosing country based on the availability of data
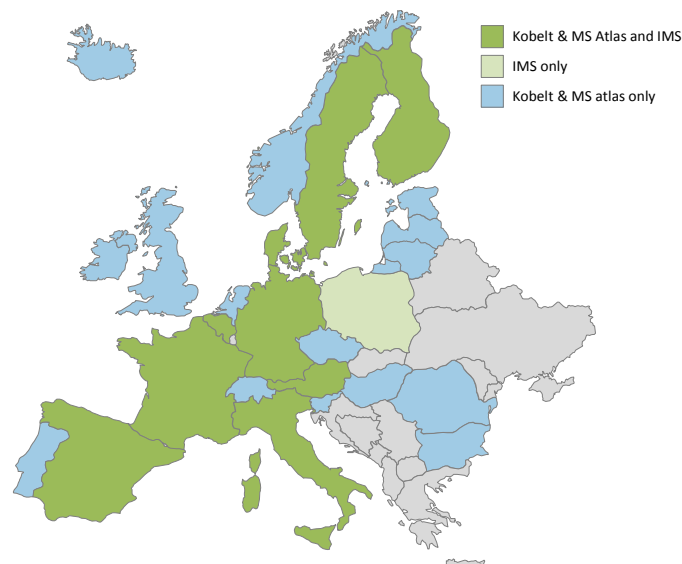
Source: CRA analysis using Kobelt (2009), MS Atlas (2008 and 2013), and analysis of IMS coverage

In order to include a broader selection of European countries, we selected several Eastern European countries out of those with prevalence data from Kobelt and MS Atlas. Poland, despite not making it past the first step, was included as it was the only Eastern European country with IMS data. Norway was also selected due to information available on the level of access from Farmastat. The selection of countries was based on income (as measured by GNI per capita) and size of country based on population. We selected three Eastern

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21   MSIF (2013) The Atlas of MS 2013, Mapping multiple sclerosis around the world. Available at http://www.atlasofms.org/./

European countries (Slovenia, Czech Republic, and Romania) so that we had examples with differences in GNI per capita and size (as illustrate in Figure 4).

Figure 4: Eastern European country selection framework
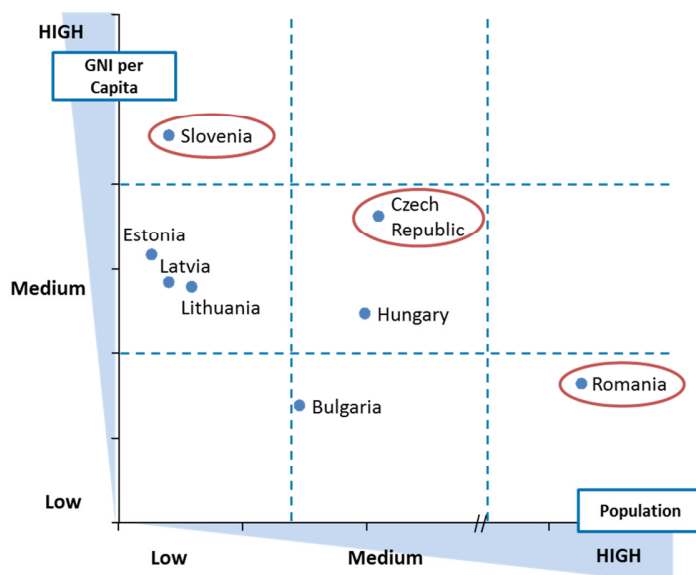
Source: CRA analysis using World Bank data 2012 (GNI per Capita & Population)

After these steps, we decided to include 15 countries listed in Table 1 as they provided a good comparison to earlier analysis (allowing us to assess improvement in access) and a wide variation in economic circumstances.

Table 1: Countries selected for analysis

1. Austria	9. Norway
2. Belgium	10. Poland
3. Czech Republic	11. Romania
4. Denmark	12. Slovenia
5. Finland	13. Spain
6. France	14. Sweden
7. Germany	15. United Kingdom
8. Italy	

For each of the countries included in the study, we have combined a variety of different sources including a literature search for country specific studies, discussions with MS societies and local stakeholders on the epidemiology, access to treatment and determinants of access to MS.

1.4. Structure of this report

The rest of the report is structured as follows:

- **Chapter 2:** Updates the data on the prevalence of the disease and examines the uptake of MS treatments.

- **Chapter 3:** Reviews the determinants of access to treatment in MS and how these have changed over the last five years.

- **Chapter 4**: Discusses the lessons learnt and policy implications to improve access to innovative treatments.

2.   Access to innovative MS treatments

To understand access to innovative MS treatments we need to estimate the number of patients with MS and the number who are receiving treatment. Over the last five years, there has been a substantial change in the availability of data, the differences in diagnosis criteria and the availability of new treatments on the market.

- We first consider the evidence regarding prevalence, comparing the most recent data to those presented in Kobelt and Kasteng (2009).

- We then turn to the estimates of usage and access. As discussed in section 1.2, we focus primarily on access disease-modifying drugs (DMDs) and a selected number of other drugs.

2.1.   Update on prevalence

The Kobelt report discusses the different diagnosis criteria that affect the estimated prevalence. The diagnosis criteria have been constantly evolving since the 1960s, and currently there are three main diagnosis criteria for MS – the McDonald criteria, the Poser criteria, and the Schumacher criteria.[22] The McDonald criteria, first published in 2001 was last revised in 2010 and has replaced the older MS diagnostic criteria such as the Schumacher criteria and the Poser criteria.[23]

The diagnosis and methods of clinical management of MS are key factors that can directly affect the use of medicines in any therapeutic area and the number of patients diagnosed with MS.

Box1: MS diagnosis criteria

MS diagnosis criteria require evidence that CNS lesions are disseminated in space (DIS), i.e., affects at least two separate areas of the CNS, and disseminated in time (DIT), i.e., there are at least two episodes of MS "attacks". Diagnosis of MS also requires that the relapses are caused by inflammatory and demyelinating lesions.

Based on the 2005 McDonald criteria, RRMS requires confirmation of DIS, e.g. through the presence of 9 lesions via MRI, and confirmation of DIT, e.g., new T1 lesions obtained in an MRI scan three months after the initial symptoms and new T2 lesions compared to the first MRI scan carried out at least 30 days after the initial clinical event. PPMS is defined as continuous progression of neurological symptoms over a year as well as two of the following three criteria: 9 cerebral T2 lesions or 4 cerebral lesions and pathological VEP, 2 focal spinal

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22   Selchen et al (2012), "MS, MRI, and the 2010 McDonald criteria: a Canadian expert commentary", Neurology 79(23); McDonald et al (2001), "Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis", Ann Neurol 50.

23   MultipleSclerosis.net (2013), "McDonald Criteria for MS".

T2 lesions, and pathological cerebrospinal fluid (CSF) findings.[24] One of the primary differences is therefore the use of MRI.[25]

The Poser criteria, meanwhile, does not even differentiate between RRMS and PPMS. The Poser criteria typically require at least one or two attacks, defined as the occurrence of symptoms of neurological dysfunction lasting more than 24 hours, and clinical evidence of one or two lesions as demonstrated by neurological examination. Additionally, paraclinical evidence may also be required.[26]

The significance of this is that the Poser criteria and McDonald criteria yield different numbers of MS patients. A study of the Poser and the 2001 McDonald criteria involving 76 patients with clinical features suggesting a new diagnosis of MS found that the number of patients classified as being diagnosed with MS under the McDonald criteria was greater than the number of patients classified under the Poser criteria. However, combining the Poser categories of clinically and laboratory definite MS resulted in more frequent diagnosis of MS compared to the McDonald criteria.[27]

The Kobelt report draws mainly on prevalence studies conducted prior to 2001 and would have been subject to the Poser criteria. A key difference between the McDonald criteria and older criteria is the integration of magnetic resonance imaging (MRI) to facilitate the diagnosis of clinical and other paraclinical methods which has led to higher estimated prevalence rates.[28] Additionally, the lack of attacks and of recurrent episodes in primary progressive forms (which are used in the Poser criteria) may have led to an underestimation in older studies.[29]

This is likely to have a bigger impact on any comparison over time than between countries. In 14 out of the 15 countries that we looked at use the McDonald criteria for diagnosis. [30] This includes: Austria, Belgium, Denmark, Finland, France, Germany, Italy, Poland, Norway,

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24   EMSP (2008), "Consensus Paper II: Basic and escalating immunomodulatory treatments in Multiple Sclerosis".

25   It should be noted that it is possible to diagnose MS using the McDonald criteria without an MRI scan, i.e. through clinical grounds alone. Polman et al (2011), "Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria", Annals of Neurology 69.

26   Poser et al (1983), "New diagnostic criteria for multiple sclerosis: guidelines for research protocols", Annals of Neurology 13(3).

27   Fangerau et al (2004), "Diagnosis of multiple sclerosis: comparison of the Poser criteria and the new McDonald criteria", Acta Neurol Scand 109(6).

28   Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. (2005), "Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria"", Ann Neurol. 58(6), 840-46.

29   Pugliattia M, Rosatia G, Cartonc H, Riiseb T, Drulovicd J, Ve´cseie L, and Milanovf I. (2006), "The epidemiology of multiple sclerosis in Europe", European Journal of Neurology, 13, 700–722.

30   MSIF (2013) The Atlas of MS 2013, Mapping multiple sclerosis around the world. Available at http://www.atlasofms.org/ and Polish Ministry of Health (2012), "Appendix B. 29: Treatment of multiple sclerosis (ICD-10 G 35)".

Romania, Slovenia, Spain, Sweden, and the United Kingdom. The Czech Republic is the exception and only uses the Poser criteria. However, countries such as, Belgium, Spain, and the UK still use both the Poser criteria in addition to the McDonald criteria. In 1983, the Poser criteria replaced the Schumacher criteria for the diagnosis of MS as it incorporated para-clinical evidence that was now available from diagnostic studies developed during the 1970s.[31] As a result, none of the 15 countries we surveyed use the Schumacher criteria. However, only the UK can diagnose MS without magnetic resonance imaging (MRI).[32,33]

Given the differences in the diagnosis criteria, any comparison over time is problematic. Prevalence depends on the survey instrument used; the inclusion of benign or early cases (which varies between countries) and diagnosis differences between countries as explained in the diagnostic criteria section.

2.1.1. Recent evidence on prevalence

There are a variety of studies investigating the prevalence of patients with MS including country-specific studies, cross-country comparisons and compendia of prevalence statistics. We undertook a literature review to identify all studies conducted from 2005 (the year of the prevalence data used in the Kobelt report). There are three international comparisons:

- Kingwell et al. (2013) have carried out a systematic review of incidence and prevalence of multiple sclerosis in Europe between January 1985 and January 2011. They observed that prevalence and incidence estimates tended to be higher in the more recent studies and were higher in the Nordic countries and in northern regions of the British Isles. They also concluded that despite the breadth of the literature on the epidemiology of MS in Europe, inter-study comparisons are hampered by the lack of standardization.[34]

- The 2013 MS Barometer produced by European Multiple Sclerosis Platform is another source of information which provides estimates of the number of people with MS.[35] The data contained in the 2013 survey were collected through an online questionnaire completed by MS patient organisations across Europe, from July to October 2013. This was an improved version of the initial questionnaire from 2008,

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[31]   Hurwitz, B. J. (2009). The diagnosis of multiple sclerosis and the clinical subtypes. Annals of Indian Academy of Neurology, 12(4), 226.

[32]   Multiple Sclerosis International Federation (2013), "Atlas of MS", accessed www.atlasofms.org on December 16, 2013.

[33]   It should be noted that even within commonly used methodology in epidemiology (e.g. the Poser criteria), the criteria used to classify patients in the respective groups (i.e. being clinical definite MS or clinical probable MS) differ between studies potentially leading to different results. Rosati G. (2001), "The prevalence of multiple sclerosis in the world: an update", Neurol Sci, 22, 117-139.

[34]   Kingwell E et al. (2013), "Incidence and prevalence of multiple sclerosis in Europe: a systematic review ", BMC Neurology, 13(128).);

[35]   European Multiple Sclerosis Platform (2013) MS Barometer 2013 – available at: www.emsp.org/attachments/article/160/MS_Barometer_2011.pdf.

reviewed for subsequent editions of the MS Barometer in 2009, 2011 and 2013 to enhance accuracy and reliability.[36]

- The "Atlas of MS" released by Multiple Sclerosis International Federation (MSIF) and the World Health Organization (WHO).[37] The MS Atlas is a database of international MS data derived from the results of a large international survey undertaken in 2008 and again in 2013. The survey was undertaken by the Multiple Sclerosis International Federation (MSIF) and MS societies in each country. It is therefore based on local studies and expert opinion.

2.1.2. Estimated number of patients

Despite some limitations in the data collection, the MS Atlas is the most comprehensive compilation of MS resources.[38] It is important to recognise that the methodology has developed since 2008.

- The 2008 survey numbers were based largely on older publications (some dating back prior to 2000), and estimates from local contacts (MSIF affiliates, neurologists, etc.).[39]
- In the 2013 survey, the MS atlas countries use a range of sources but favours peer-reviewed publications reporting national or local level epidemiology and data from local/national patient registries.

Epidemiology data from the MS atlas 2008 and 2013 surveys for the countries selected in the first section are summarised in Table 2. The table also illustrates Kobelt's prevalence number and the growth (%) from Kobelt and the MS atlas 2013. Kobelt took a different approach. Kobelt used local studies to develop prevalence for similar ethnic/geographic groups and derived an average prevalence rate per specific age group and then applied this to the population in each country.[40]

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[36]   Ibid.

[37]   MSIF (2013) The Atlas of MS 2013, Mapping multiple sclerosis around the world. Available at http://www.atlasofms.org/./

[38]   MSIF (2013) The Atlas of MS 2013, Mapping multiple sclerosis around the world. Available at http://www.atlasofms.org/

[39]   Interview with MSIF MS atlas project.

[40]   Kobelt did not use the MS Atlas numbers as most of the numbers in the MS Atlas came from the published studies and hence considers that they are already taken into account in the estimates.

Table 2: MS atlas prevalence rate per 100,000 change compared to Kobelt 2008 prevalence rate

	Prevalence rate (per 100,000)		
	Kobelt 2008	**Atlas 2008**	**Atlas 2013**
Austria	93	100	140
Belgium	90	88	100
Czech Republic	79	130	160
Denmark	129	122	227
Finland	131	100	105
France	75	80	94.7
Germany	137	149	149
Italy	81	90	113
Norway	166	125	160
Poland	59	120	n/a
Romania	38	31	30
Slovenia	81	151	120
Spain	80	59	102
Sweden	128	100	189
United Kingdom	127	110	164

Source: CRA analysis using Atlas of MS, epidemiology data 2008 and 2013; Note: We opted to use Kobelt's cases per 100,000 population over cases per 100,000 >19 population due to pool average prevalence used in the access section of the write-up.

As expected the changes in prevalence in many countries are very significant. This reflects that the 2008 estimates were based on different diagnosis criteria and (in the case of Kobelt) were not country specific and are likely to have been a significant under-estimate of the number of patients with MS. We therefore focus primarily on differences in access between countries rather than comparisons over time.[41]

Using the MS Atlas prevalence rates we can calculate the number of patients with (all forms of) MS as presented in Table 3.

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[41] This conclusion is similar to that of Kingwell et al. Firstly, Kingwell et al stated that the more recent studies used in their literature review were generally of higher quality and used the more recent diagnostic criteria. Secondly, they concluded that any comparison over time is likely to be problematic although it is reasonable to conclude that more recent studies tended to show a higher prevalence than the older studies.

Table 3: Total number of patients with MS (2013)

Country	Total number of patients with MS
Austria	12,500
Belgium	12,200
Czech Republic	16,800
Denmark	12,700
Finland	5,700
France	80,000
Germany	122,000
Italy	68,800
Norway	8,000
Poland	45,000
Romania	6,400
Slovenia	2,500
Spain	42,900 [42]
Sweden	18,200
United Kingdom	103,700

Source: CRA analysis using MS Atlas 2013 and other sources [43] Note: Total number of patients with MS calculated using country prevalence and respective populations and rounded to the nearest 100.

As mentioned in section 1.1, the European Multiple Sclerosis Platform has also published their latest version of the MS Barometer in 2013 which also includes their estimated number of people with MS. The estimated total number of people with MS using the MS barometer is similar to our calculated number. Indeed, the MS atlas and MS Barometer estimates are relatively similar with an aggregate difference of ~1%.

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[42]   Whilst the MS Atlas 2013 provides an estimate of 42,900 patients, the Spanish MS society Esclerosis Múltiple España reported that the number patients is probably higher (i.e. 46000 instead of 43000).

[43]   Austria: 12,689 sourced from Österreichischer Patientebericht (ÖPB); Belgium: 12,191 calculated using Belgian population and prevalence 110/100,000 prevalence from CTG report on MS ; France: Foundation pour l'aide a la recherché sur la Sclerose en Plaques (ARSEP). Poland number from MS atlas 2008 as there is no 2013 number available from the MS atlas 2013.Slovenia number come from estimates from Healthcare providers validated by the Slovenia MS society.

2.2.   Patient access to innovative MS treatments

In order to identify the number of patients currently on treatment, we followed the approach developed in Kobelt (2009). This uses data on volume of medicines used in each country (using IMS reported unit sales in 2013, or using an alternative data source).[44] We then used average dose to calculate the number of patients using each medicine. This has a number of assumptions:

- We assumed that every patient is on the treatment for the full year.[45]
- We determined the average dose for a patient on each medicine using the EMA recommended dosages from each medicine's respective 'Summary Of Product Characteristics'.
- We divided the number of packs by the average dose for a patient on those medicines. As we did not have data in every country at the pack level, when calculating patient number for drugs that are known to have multiple pack types, we used the pack that had the highest proportion of sales.[46]

Where IMS data was not available or had limited coverage, we used estimates in the literature or patient number estimates from national MS societies. The 2013 number of patients receiving treatment in each of the selected countries is listed in table 4.

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[44]   Seven DMDs are included in the analysis including all MS interferons (Avonex, Betaferon, Rebif, and Extavia), glatiramer acetate (Copaxone), natalizumab (Tysabri), and fingolimod (Gilenya). Although DMDs can be available as a combination therapy, they are never used in combination with any other DMD. Fampridine (Fampyra) is a symptomatic treatment and may be used laterally with a DMD, as such, the number of patients using Fampyra might overlap with those using DMDs and therefore Fampyra is not analysed in the same way as the DMDs.

[45]   In reality, some patients will only be on the medicine for a proportion of the year. These figures will therefore under-estimate the number of patients treated.

[46]   In these countries, we used Denmark as a reference.

Table 4: Patients receiving treatment in 2013

Country	Patients receiving treatment	Analysis based on
Austria	6,300	*IMS data*
Belgium	7,200	*IMS data*
Denmark	5,600	*IMS data*
Czech Republic	6,500	*Estimate from local MS society*
Finland	3,500	*IMS data*
France	32,000	*GERS data*
Germany	84,700	*IMS data*
Italy	32,200	*IMS data*
Norway	4,200	*Farmastat*
Poland	5,800	*IMS data*
Romania	2,500	*Estimate from local MS society*
Slovenia	1,300	*Estimate from HCP in Slovenia*
Spain	21,600	*IMS data*
Sweden	7,100	*IMS data[47]*
UK	21,400	*Estimate from local MS society & CRA calculation*

Source: CRA analysis using IMS data and other sources. Note: Numbers are rounded to the nearest 100.

We have compared our calculated number with the number of patients with MS receiving treatment according to the MS barometer (this was calculated using the % of patients receiving treatment and the number of patients with MS) and apart from a few countries (Italy, Czech Republic, Austria, and Sweden), the differences are small.

2.2.1. Patient access to innovative MS treatments

In order to estimate patient access to treatment, we calculated the proportion of the MS patient population receiving treatment using the absolute number from 2013 (from table 4) and the total population with MS in 2013.

We observed that the difference in access to treatment has increased since 2008 with a catch up from poor performers such as the UK and Eastern European countries (e.g. Romania, Czech Republic). However, the best performers have also increased patient access. The result of this is that whereas Kobelt found a range of 6% to 58% for the set of countries, we find a range from 13% to 69%. As illustrated in Figure 5, significant inequalities in access still remain across Europe with access to treatment as high as 69% in Germany and only around 13% in Poland.

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[47]   Sweden uses an additional product off-label known as Mabthera to treat MS patients. Calculations therefore include 6719 patients on DMDs + 400 patients on Mabthera.

Figure 5: Proportion (%) of MS total patients receiving DMDs in 2013

Country	%
Germany	69%
Finland	62%
Belgium	59%
Slovenia	53%
Norway	52%
Austria	51%
Spain	50% [1]
Italy	47%
Denmark	44%
France	40%
Romania	39%
Sweden	39% [2]
Czech Rep	39%
UK	21%
Poland	13%
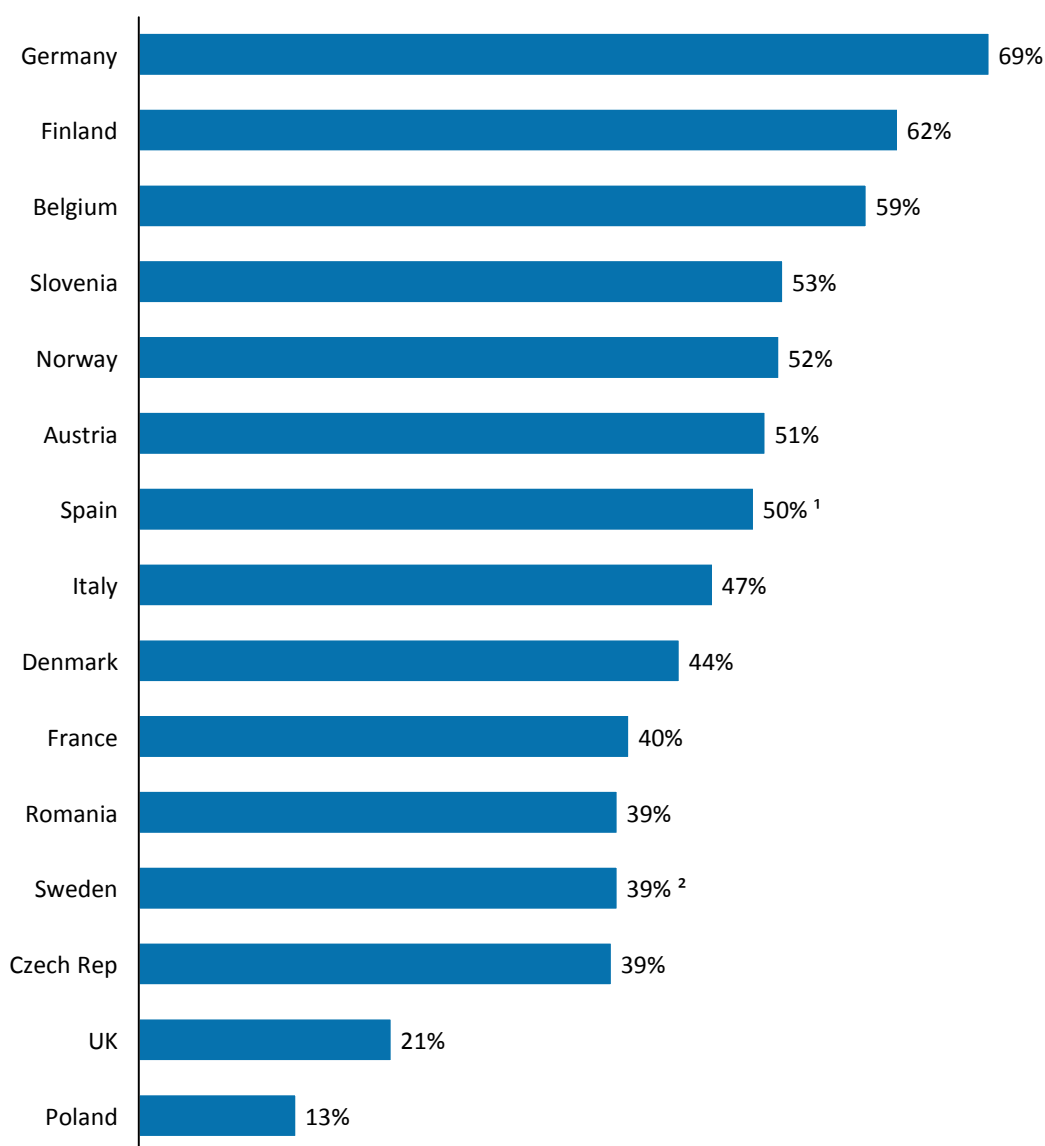
Source: CRA analysis using IMS 2013, local MS societies, and MS atlas 2013

1 The Spanish MS society reports that the total MS patient population is higher (i.e. 46000 instead of 43000). The result of this would be to lower our access calculation to 46%.

2 According to national Swedish MS Society guidelines, treatment is only provided to patients suffering from relapsing remitting MS (RRMS) and not to patients with progressive forms of MS (PPMS, SPMS) since current DMDs have no or only limited proven efficacy on disease progression for these patients, which reduces the figure for the total number of patients on DMDs.

2.2.2. Access to innovative MS treatments for sub-types of MS patients

It is important to note that the calculation of access depends critically on the definition being used. As only patients with RRMS and SPMS are eligible for DMDs a better measure of access would account for the types of patient. In some countries studies exist that have looked at the level of access for different sub-populations.

However, only limited data is available on access to DMDs for specific sub-types of MS patients and only figures for France, Germany, Italy, Spain and the UK are available in the literature. See below. Additional calculations allow us to derive a figure of 75% access in Sweden.[48] Figure 6 shows that the RRMS patients generally have much better access to DMDs than other patient sub-groups (i.e. SPMS, PPMS, PRMS) with access ranging from 59% in the UK to 91% in France.

Figure 6: % of RRMS patients receiving DMDs
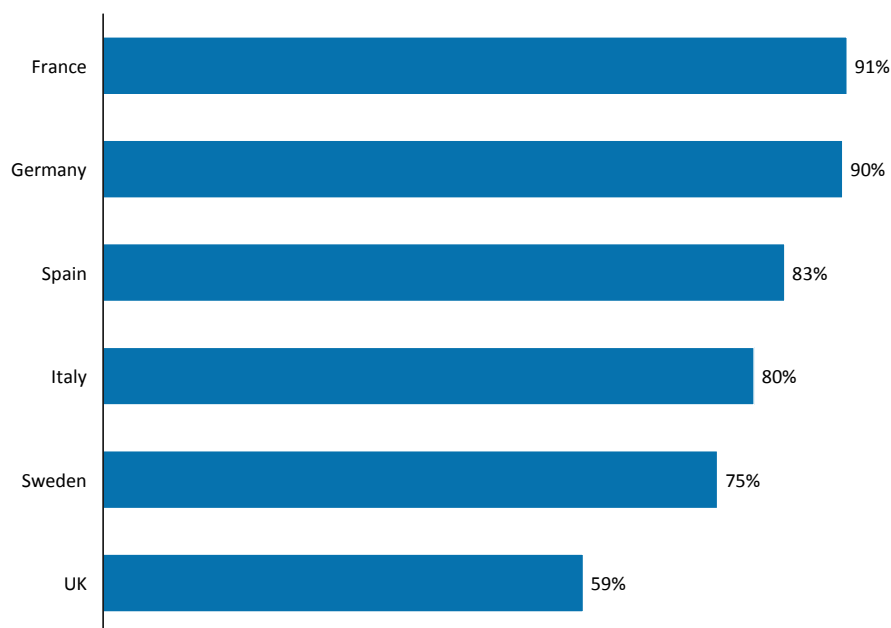
Source: CRA Analysis using Datamonitor (Multiple sclerosis survey – November 2011) and CRA calculation based on IMS data for Sweden for RRMS treated patients only.

This is likely to be particularly important where countries have their national treatment guideline focusing on a particular MS patient sub-population. For example, in Sweden according to Swedish MS Association (SMSS) which issues recommendations for the use of immunomodulatory therapy, approximately 75% of patients with relapsing- remitting multiple sclerosis meet the criteria for therapy, as opposed to a small percentage of those with secondary progressive multiple sclerosis.[49] This is also the case where the composition of patients differs from country to country. For example, Sweden has a particularly high level of SPMS patients.[50] In fact, in Sweden there is a target of treating 75% of patients with RRMS, suggesting that high levels of access are being achieved.

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[48]   There is a total of 7119 MS patients treated on DMD. Of those, 6819 patients have RRMS (7119-300). Out of a total 9100 prevalent patient population, this mean 75 % of RRMS patients treated (6819/9100)

[49]   Swedish National Board of Health and Welfare Publikationsservice (2012) Quality and Efficiency in Swedish Health Care Regional Comparisons 2012, available at www.socialstyrelsen.se/publikationer

[50]   Pozzilli, C., Romano, S., & Cannoni, S. (2002). Epidemiology and current treatment of multiple sclerosis in Europe today. Journal of Rehabilitation Research and development, 39(2), 175-186.

2.2.3. Comparison by type of product

It is also interesting to distinguish between the access to particular types of products. The range of products available for MS patients has also changed since Kobelt and Kasteng (2009). Three new drugs have been approved for treatment of multiple sclerosis. The EMA approval dates are set out in Table 5 below. These include:

- Two new disease-modifying drugs (DMD) have been included in our analysis. This include *Extavia* a reformulation of an Interferon beta-1b used to treat the relapsing-remitting and secondary-progressive forms of multiple sclerosis (MS) and *Gilenya* (Fingolimod), an immunomodulating drug used to reduce the rate of relapses in relapsing-remitting multiple sclerosis. More recently, two additional oral DMD treatments have received EMA approval including *Aubagio* (Teriflunomide) in March 2013, and *Tecfidera* (Dimethyl Fumarate) in February 2014 but these have not reached the market. *Lemtrada* (Alemtuzumab), also a DMD treatment is administered via IV infusion has also been approved by the EMA in September 2013.

- *Fampyra* (Fampridine), a potassium channel blocker was also recently launched on the market in some European countries to improve walking speed for some patients with MS. Within Europe, the IMS data used in this study only report the use of Fampyra in Germany and Finland.[51]

The EMA approval dates are set out in Table 5 below.

Table 5: Drugs used for the treatment of MS included in the analysis

Generic name	Brand name	EMA Approval
Interferon beta-1b	Betaferon⊛	1995
Interferon beta-1a	Avonex⊛	1997
Interferon beta-1a	Rebif⊛	1998
Glatiramer acetate	Copaxone⊛	2002
Natalizumab	Tysabri⊛	2006
Interferon beta-1b*	Extavia⊛	2008
Fingolimod*	Gilenya⊛	2011

*Source: Adapted from the European Multiple Sclerosis Platform and the European Medicines Agency,*Not included in Kobelt and Kansteng (2009)*

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[51]   Another symptomatic treatment called Sativex (nabiximols) is currently available in various European markets being was first approved in the UK in 2010 although uptake is very low

As illustrated in Table 6, there are currently five DMDs used as first line treatments for RRMS (the key subcategory of MS requiring DMDs), of which four are interferons, and two DMDs used as second line treatment.[52]

Table 6: First vs. second line treatments for relapsing-remitting multiple sclerosis

First line treatments for RRMS	Second line treatment for RRMS
• Avonex® (Beta interferon 1a) • Rebif® (Beta interferon 1a) • Betaferon® and Extavia® (Beta interferon 1b) • Copaxone® (Glatiramer acetate)	• Gilenya® (Fingolimod) • Tysabri® (Natalizumab)

Source: UK MS Society[53]; Note: This does not vary by country

However, this is expected to change in the near future with the recent entry of several new treatments including two new DMDs which have just entered the market in late 2013 and early 2014 and were therefore not included in our analysis:

- Aubagio® (Teriflunomide) – approved by the EMA in March 2013;

- *Lemtrada*® (Alemtuzumab) – approved by the EMA in September 2013;

- Tecfidera® (Dimethyl fumarate) – approved by the EMA in February 2014;

Additional innovative symptomatic treatments (i.e. non DMDs) – used in parallel with DMDs to reduce symptoms associated with MS and therefore not contributing directly to the calculation of additional patient numbers – were also excluded from our analysis such as:

- Fampyra® (Fampridine);

- Sativex® (Nabiximols).

Based on this classification, we can assess uptake of newer second line therapies (Fingolimod and Natalizumab) versus first line treatments. From this we can clearly see which countries provide the highest level of access to the newer treatments as illustrated in Figure 7. We observe that the Scandinavian countries provide better access to innovative second line treatment in Europe (Norway 39%, Sweden 30.4%, Denmark 29.5%), whereas Eastern European countries have significantly lower proportions. In some countries, such as Sweden, Mabthera (Rituximab) is widely used off-label to treat difficult cases of multiple sclerosis[54] (400 patients in Sweden), however, as it is off-label use, we have not taken it into account in the analysis below.

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52   Mssociety.org.uk - Disease modifying drugs (MS Essentials 06), retrieved from http://www.mssociety.org.uk/ms-resources/disease-modifying-drugs-ms-essentials-06.

53   Ibid.

54   Hauser, S. L.et al (2008). B-cell depletion with rituximab in relapsing–remitting multiple sclerosis. New England Journal of Medicine, 358(7), 676-688.

Figure 7: Proportion of all MS patients receiving innovative treatments (%)
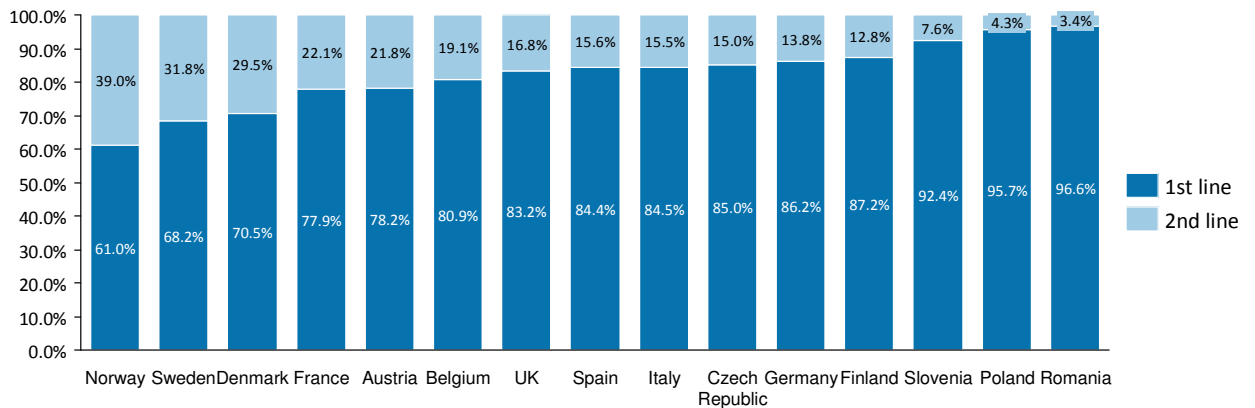
Source: CRA analysis using IMS 2013 (Austria, Belgium, Denmark, Finland, Germany, Italy, Poland, Spain, Sweden), GERS (France), Farmastat (Norway), MS national Progam (Romania), CEE average (Slovenia)

2.2.4. Ranking of patient access

We can also look at patient access in terms of how countries rank. Since the Kobelt report, there has been a shift in the selected countries' relative rank in terms of coverage of MS products. The most notable change in ranking is with Germany moving from 7th to 1st place, whilst Scandinavian countries such as Denmark and Sweden have potentially seen a decrease in access as illustrated in Table 7. This shows a change in rank for most countries with those previously providing less coverage moving up. Germany and Finland exhibited the biggest changes in access, moving from 7th to 1st rank, and 10th to 2nd respectively. The biggest fall in rank are Austria and France moving from 1st to 6th, and 3rd to 10th place respectively.

Table 7: Country rankings for access to MS

Country	2008 rank (Kobelt 2009)	2013 rank (CRA 2013 analysis)	
Germany	7	1	↑
Finland	10	2	↑
Belgium	2	3	↓
Slovenia	8	4	↑
Norway	11	5	↑
Austria	1	6	↓
Spain	6	7	↓
Italy	4	8	↓
Denmark	5	9	↓
France	3	10	↓
Romania	15	11	↑
Sweden	9	12	↓
Czech Rep	12	13	↓
UK	14	14	-
Poland	13	15	↓

Source: CRA analysis using IMS 2013, local MS societies, MS atlas 2013, and Kobelt 2009

Table 8 shows a comparison between the CRA ranking and the relative ranks from a 2010 report for the UK Department of Health on the access to MS treatments (not limited to DMDs). There is some degree of consistency between the two sets of results with Germany figuring first on both lists and the UK last although there are also some big differences such as Denmark and Sweden featuring significantly higher on the 2010 list than on ours.

Table 8: Comparison of CRA rankings with 2010 study rankings

Country	Richards rank (2010 report)	2013 rank (CRA 2013 analysis)
Austria	7	2
Denmark	2	5
France	6	7
Germany	1	1
Italy	3	4
Spain	5	3
Sweden	4	7
UK	8	8

Source: CRA analysis using IMS 2013, local MS societies, MS atlas 2013, and Kobelt 2009; and Richards M CBE (2010), "Extent and causes of international variations in drug usage", A report for the Secretary of State for Health by Professor Sir Mike Richards CBE

2.3.   Summary

From the data analysed above, we can make the following observations

- There has been an improvement in the number of patients with access to treatment in all countries. On average the number of patients with access has increased by 50%. Even allowing for large increases in reported prevalence the level of access has also increased significantly;

- The difference in access to treatment between countries has not narrowed however. Even though there has been a significant catch up from the previously poor performers such as the UK and Eastern European countries, overall the range in the level of access has increased. Significant inequalities in coverage still remain with access to treatment as high as 69% in Germany and only around 13% in Poland;

- However, the ranking of countries in terms of access to innovative products differs significantly. Norway, Sweden and Denmark provide the highest levels of coverage of the new medicines (ca. 39-30%), whereas Eastern EU countries have significantly lower proportions.

3. Determinants of access to treatment in MS

In this chapter, we consider the factors that explain the differences in access presented in the last chapter. There are a variety of potential explanatory factors that might have an influence over the reimbursement and prescription of innovative treatments for MS patients and could potentially vary across countries. These include:

- Diagnosis and clinical management of MS such as the availability of neurologists or differences in treatment guidelines for MS;

- Differences in the reimbursement process and patient eligibility for treatment including restrictive HTA decisions and market access delays;

- The affordability of MS drugs.

- The use of patient registries or databases.

3.1. Diagnosis and clinical management of MS

In many countries, MS remains largely misunderstood with even GPs admitting their knowledge is limited which means both diagnosis of the disease and clinical management of MS can vary within countries as well as across the continent.[55] A potentially significant barrier to treatment is when patients are not diagnosed or referred to a specialist in a timely fashion. We explore several clinical management factors that have been identified as having a potential impact on access to treatment, namely:

- Availability of qualified healthcare professionals such as specialised MS centres, availability and density of neurologists and number of specialised MS nurses.

- Differences in clinical management of MS and the existence and impact of treatment guidelines for MS.

3.1.1. Availability of qualified healthcare professionals

A number of studies indicate that the availability of specialised MS centres, specialists within these centres and supporting healthcare professionals could represent significant barriers to patients accessing DMDs.

A common proxy for the healthcare infrastructure is the number of neurologists. Neurologists are typically the main decision makers for a patient's MS treatment. Indeed, as illustrated in Figure 8, we can observe a correlation between the number of neurologists per 100,000 population and access to DMDs.
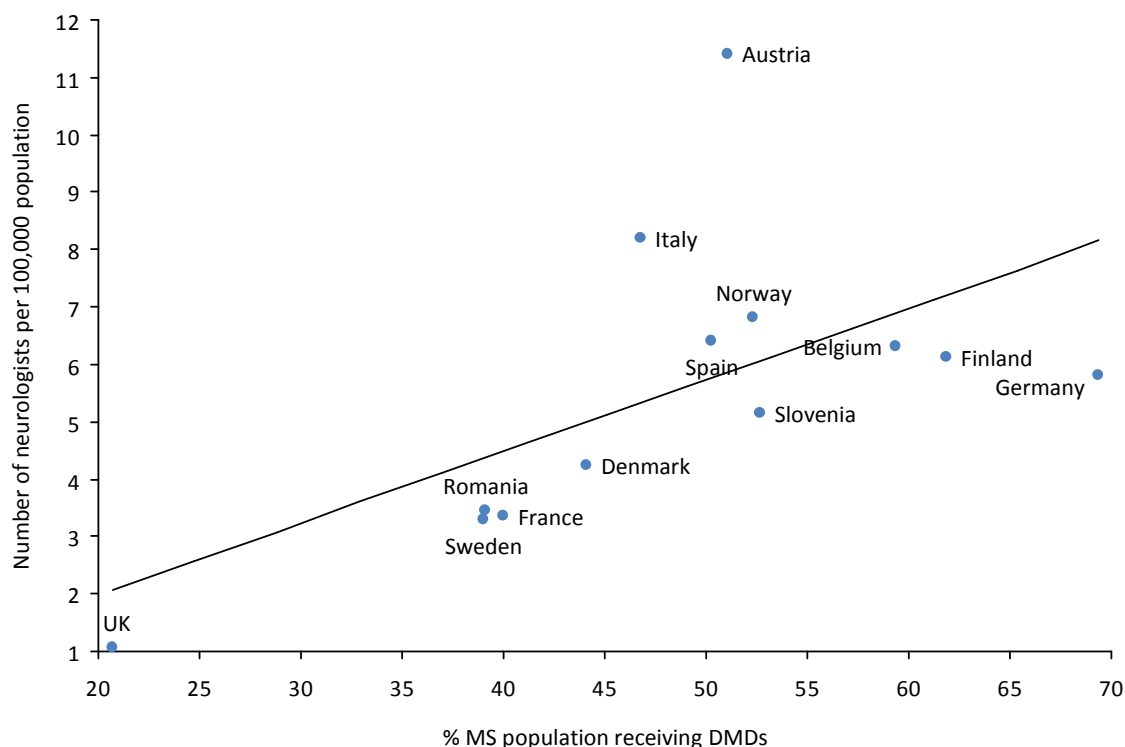
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[55] UK MS Society (2011) The MS Register, available at http://www.ukmsregister.org/Portal/Home

Figure 8: Number of neurologists per 100,000 specialised in MS[56] vs. percent of MS population receiving DMDs, 2013

Source: Multiple Sclerosis International Federation (2013), "Atlas of MS", accessed at www.atlasofms.org

Access to a neurologist is seen as particularly problematic in some member states. For example, in the UK (which continues to have low levels of access), the number of neurology consultants in the UK has risen from 1 per 200,000 people in 1998 to 1 per 100,000 in 2013 but remains substantially lower than in other European member states.[57] Evidence from within the UK illustrated how this might act as a barrier. In Northern Ireland, where access is higher, most people with MS are routinely invited every six months to see a neurologist or MS nurse for a review. By ensuring that people with MS are regularly seen by a specialist their treatment options are under continual and ongoing assessment and they are more likely to get the information they need, to discuss issues such as side effects, or have other services

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[56]   The MS Atlas defines a neurologist as someone whose professional interests and activities are related exclusively/specifically to the care of people with MS. He/she runs a clinic or service for MS patients separate from other neurological practice, provides overall management of care, neurologic testing and evaluation, and prescribes medications and monitors their effectiveness.

[57]   "Access to treatments and services for people with MS in the UK" Advances in Clinical Neuroscience and rehabilitation, Supplement to ACNR Volume 12 Issue 2 MAY/JUNE 2012 ISSN 1473-9348; Multiple Sclerosis International Federation (2013), "Atlas of MS", available at www.atlasofms.org, accessed December 16, 2013.

signposted.[58] More broadly, there is also considerable variation in specialised neurology and neurological rehabilitation services.[59]

However, neurologists are not the only healthcare professionals that can assist in providing access to MS treatment. There are a number of studies that have highlighted the role that nurses play in identifying MS symptoms and the management of any adverse events of treatment.[60] In addition to assisting in the management of the disease, nurses are also important as they encourage the use of new treatments.[61]

Additionally, nurses can also assist in patient education and support, which improves adherence, as the nurses have the opportunity to observe changes in the patient's condition, discuss this with patients and report back to the neurologist with updates regarding patient treatment and compliance. Adherence is particularly important for MS as effectiveness of DMD treatment depends on adherence. In reality DMD-treated patients miss 30% of doses. The 6-month discontinuation rate is as high as 27%.[62] Although treatment adherence is influenced by many factors (socio-economic situation, health care and caregivers, disease, treatment and patient characteristics), patient education and support improves adherence in general. Studies have shown that patients participating in disease management programmes have a 10% higher rate of adherence. This data suggests that ensuring that patients are enrolled in the appropriate product support programme when they start therapy is important.[63]

3.1.2. Clinical management of MS

Another potential explanatory factor for differences in access across countries could be differences in clinical guidelines. This could explain differences in initiation of therapy. For example, countries may require a different number of relapses before DMD is initiated for MS. Pozzilli et al noted on average patients in Europe experienced 4 relapses before being initiated on treatment. However, the number varied across countries in Europe, with the Mediterranean countries (Spain, Greek, and Italy) starting patients on DMDs after fewer relapses than in the Northern European countries. The result is that patients with SPMS are treated later in the Northern European countries. These observations were based on a forum

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58   "A lottery of treatment and care – MS services across the UK"

59   "MS Barometer 2013 Widespread health inequalities revealed"

60   "Management and Care – The Changing Landscape of Multiple Sclerosis" a report by Cindy Lee and Pat Wong

61   "Disparities in Nursing of Multiple Sclerosis Patients – Results of a European Nurse Survey" Hans-Peter Hartung, Vicki Matthews, Amy Perrin Ross, Dorothea Pitschnau-Michel, Christoph Thalheim and Nicki Ward-Abel6 on behalf of the Multiple Sclerosis-Nurse Empowering Education (MS-NEED) Study Group

62   "Drug adherence and multidisciplinary care in patients with multiple sclerosis: Protocol of a prospective, web-based, patient-centred, nationwide, Dutch cohort study in glatiramer acetate treated patients (CAIR study)" Jongen et al. BMC Neurology 2011, 11:40 http://www.biomedcentral.com/1471-2377/11/40

63   "Optimizing Adherence to Multiple Sclerosis Therapies: Managing Tolerability and Monitoring Safety" Barry Singer, MD; Sylvia Lucas, MD, PhD; Kiren Kresa-Reahl, MD; Amy Perrin Ross, APRN, MSN, CNRN, MSCN; Patricia Blake, MSCN, RN. International Journal of MS Care

that occurred in 1999.[64] We have not been able to identify more recent data that allows us to test if those observations persist today.

European treatment guidelines

With the exception of France which was not included in the EMSP survey, diagnosed MS patients in the 14 out of 15 case study countries can be treated according to the recommendations outlined by the EMSP.[65] The EMSP Consensus Paper II defines MS according to the McDonald 2005 revised criteria and discusses the clinical evidence available on beta-interferons, Glatiramer acetate, and Natalizumab but does not explicitly recommend when treatment should be initiated or which ones should be used first, beyond what is stated in the EMA indication.[66] As such, there are no stringent European treatment guidelines on MS DMDs apart from the EMA approvals.

Country-specific clinical guidelines

To investigate this further, we have examined a selection of our case study countries (Belgium, France, the UK, the Czech Republic, and Sweden). Although there are differences in clinical guidelines, the recommendations are broadly similar in most cases and seem unlikely to have a significant impact on usage. The exception is the Czech Republic where the guidelines appear significantly more restrictive.

For example, all five countries except for the Czech Republic recommended patients to have experienced at least two attacks in the last two years before initiation on beta-interferons or Glatiramer acetate. The Czech Republic recommended two attacks in the last year or three attacks in the last two years before initiating patients on the aforementioned DMDs. Natalizumab can be used in certain treatment-naïve patients in all five countries, as can Fingolimod except for the UK, which requires the use of a beta-interferon for at least a year.

There are also slight variations in terms of the maximum Expanded Disability Status Scale (EDSS) at which patients are still eligible for treatment. In France, EDSS does not limit the MS patient's DMD eligibility. Patients in the UK are eligible for treatment if they have an EDSS of 6.5 or less, in Belgium the maximum EDSS is 5.5 or 6.5, while in the Czech Republic the maximum EDSS is 4.5 for reimbursement for beta-interferons and Glatiramer acetate. Additionally, the MS guidelines in Sweden and the UK do not recommend DMDs for patients whose EDSS is 7.0 or higher.

Despite these slight differences, there is little evidence to conclusively link differences in clinical guidelines with access to MS treatment.

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[64]   Pozzilli et al (2002), "Epidemiology and current treatment of multiple sclerosis in Europe today", JRRD 39(2).

[65]   EMSP (2008), "Consensus Paper II: Basic and escalating immunomodulatory treatments in Multiple Sclerosis".

[66]   EMSP (2008), "Consensus Paper II: Basic and escalating immunomodulatory treatments in Multiple Sclerosis".

Belgium

The Belgian MS society recommends using beta-interferons and Glatiramer acetate as first line treatments for RRMS, and Natalizumab, Fingolimod, or Mitoxantrone as second line treatments. It notes that Novantrone use is typically limited due to its poor safety profile.[67]

To be eligible for RIZIV/Inami reimbursement for beta-interferons (Avonex, Betaferon, Rebif, or Extavia) or Glatiramer acetate (Copaxone), patients need to be classified as RRMS based on two laboratory tests, have an EDSS of 5.5 or less, and have had at least two attacks in the last two years. Patients with SPMS, classified based on two laboratory tests, have an EDSS of 6.5 or less, and at least two attacks in the last two years, can be treated with Betaferon, Rebif, or Extavia. Patients that experience a neurologic episode, i.e. a Clinically Isolated Syndrome (CIS), and significant MRI abnormalities (e.g. 9 lesions) and other characteristics that put them at increased risk of developing MS can be treated with Avonex, Betaferon, Extavia, or Copaxone. Patients can switch treatment if the number of attacks increases or the level of disability increases over the course of one year of treatment.[68]

Patients are eligible for RIZIV/Inami reimbursement of Natalizumab or Fingolimod if they are over 18 years old, have RRMS as confirmed by two laboratory tests, have an EDSS of 6.5 or less, and fulfils one of the following conditions: [69]

- Inadequately responded to at least one year of treatment with a beta-interferon, during which there was at least one debilitating attack and demonstrated at least 9 T2 hyperintense lesions or at least one gadolinium lesion through a brain MRI in the last 6 months;
- Has already been treated with the other second line drug, i.e. Natalizumab or Fingolimod; or
- Has severe RRMS, defined by at least two disabling relapses in one year, and an MRI in the last 6 months that demonstrated at least one gadolinium lesion or a significant increase in T2 lesions

The Belgian MS Society does not provide a DMD stopping criteria.

Czech Republic

The beta-interferons and Glatiramer acetate are reimbursed by the Czech healthcare system for patients with RRMS, who have had two attacks in the last year or 3 attacks in the last two years, and with an EDSS of 4.5 or less. It is also indicated for patients with a single demyelinating event and at a high risk of MS. Approval is required if treatment is to be continued for more than four years, and treatment should be stopped if the patient experience

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[67]   National Belgian MS Society (2013), "Current treatment", available at http://www.ms-sep.be/nl/medische-info/huidige-behandeling, accessed January 6, 2014.

[68]   National Belgian MS Society (2013), "Current treatment", available at http://www.ms-sep.be/nl/medische-info/huidige-behandeling, accessed January 6, 2014.

[69]   National Belgian MS Society (2013), "Current treatment", available at http://www.ms-sep.be/nl/medische-info/huidige-behandeling, accessed January 6, 2014.

two or more severe relapses a year, have a one point increase in the EDSS in a year, or lose the ability to walk.[70]

Natalizumab is reimbursed by the Czech healthcare system for patients with RRMS who suffered two to three attacks in the last two years despite treatment with beta-interferons or Glatiramer acetate. It is also reimbursed for use among patients with rapidly evolving severe RRMS who suffered at least two relapses in the last year and with evidence of gadolinium-enhancing lesion or a significant in T2 lesion load.[71]

Fingolimod's reimbursement conditions are the same as for Natalizumab, with the addition that reimbursement will be discontinued if the patient fails to respond to treatment, for example as measured through an EDSS increase of one in a year, or if the patient experiences two severe attacks in a year or three attacks in two years while on therapy.[72]

France

The French MS societies did not provide any clinical recommendations but the Haute Autorite de Santé (HAS) has produced a clinical guideline on MS in 2006[73]. It is primarily for RRMS and early progressive phases (SPMS) patients that DMDs are seen as the most beneficial. The three Interferons (IFN) beta and Glatiramer acetate and Azathioprine are the main treatments recommended for RRMS. For more aggressive forms of MS, Elsep® (mitoxantrone) is recommended to reduce the number of relapse.

UK

NICE typically issues treatment guidelines for various diseases in the UK. NICE concluded in 2001 that the beta-interferons and Glatiramer acetate were not cost-effective. In 2002 a risk sharing scheme was agreed between the manufactures and the NHS, where the NHS would fund MS treatments and assess the cost-effectiveness of these drugs retroactively based on the collected real world evidence. For patients to be eligible for NHS-funded MS treatment, they must fulfil the criteria as specified by the Association of British Neurologists (ABN), the most basic of which is that patients should be ambulant (maximum EDSS 6.5) and at least 18 years old.[74]

The ABN guidelines state that RRMS patients are eligible for beta-interferons or Glatiramer acetate. RRMS is defined as a patient with active MS with relapsing onset, where active MS is defined by two "clinically significant" relapses in the previous two years. The guidelines do

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70   Lecich   website,   available   at   http://www.olecich.cz/modules/medication/detail.php?code=0026252&tab=prices, accessed January 6, 2014.

71   Lecich   website,   available   at http://www.olecich.cz/modules/medication/detail.php?code=0027184&tab=prices, accessed January 6, 2014.

72   Lecich   website,   available   at   http://www.olecich.cz/modules/medication/detail.php?code=0168462&tab=prices, accessed January 6, 2014.

73   Haute Autorité de Santé (HAS) – Guide affection de longue durée – Sclérose en place - Septembre 2006

74   ABN (2009), "Revised (2009) Association of British Neurologists' guidelines for prescribing in multiple sclerosis"; NICE issued MS treatment guidelines in 2003, which is currently being revised, but do not provide recommendations on DMD use or concrete diagnosis criteria.

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not specify what constitutes a clinically significant relapse. The ABN guidelines also recommend that relapsing forms of SPMS should be treated but does not specify which DMDs should be used, and notes that there is nothing indicated for PPMS. In addition to recommending that RRMS and SPMS patients be treated with DMDs, the ABN guidelines also note that neurologists may consider treating patients with clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of developing MS.[75] It is possible that the requirement of relapses to be "clinically significant", which is not clearly defined by the ABN, rather than MRI evidence as required by the McDonald criteria causes physicians to be more cautious in prescribing DMDs, resulting in lower DMD access in the UK.

NICE and ABN recommendations for Natalizumab are the same. Both guidelines recommend Natalizumab for RRMS patients with rapidly evolving and severe MS, defined as patients with at least two disabling attacks in one year and with at least one gadolinium-enhancing lesion or a significant increase in T2 lesion load. Neither set of recommendations specify it as a second-line treatment.[76]

As the ABN guidelines were published before Gilenya's launch, there is no discussion of the treatment criterion for Gilenya. However, NICE has appraised Gilenya and recommended it for use for highly active RRMS in adults only if the relapse rate did not decrease compared to the previous year despite treatment with a beta-interferon. Positive recommendation is also contingent on a discount provided as part of the patient access scheme.[77]

The ABN does not provide mandatory stopping criteria, recognizing that it is difficult to determine conclusively that a DMD provides no benefit. The ABN does provide scenarios that are suggestive of loss of benefit, for example, the development of non-relapsing SPMS with an EDSS of seven or more, that should be considered when deciding treatment discontinuation.[78]

Sweden

In the early 2000s, the Swedish Multiple Sclerosis Registry showed that many RRMS patients were not treated, whereas a large number of SPMS patients were treated despite more available therapies for RRMS. As a result, the Swedish healthcare system has focused on treating more RRMS patients with the appropriate DMDs.[79] Currently; the Swedish MS

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[75]   ABN (2009), "Revised (2009) Association of British Neurologists' guidelines for prescribing in multiple sclerosis".

[76]   ABN (2009), "Revised (2009) Association of British Neurologists' guidelines for prescribing in multiple sclerosis"; NICE (2010), "Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis", TA 127.

[77]   NICE (2012), "Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis", TA 254.

[78]   ABN (2009), "Revised (2009) Association of British Neurologists' guidelines for prescribing in multiple sclerosis".

[79]   Swedish National Board of Health and Welfare (2012), "Quality and efficiency in Swedish health care: regional comparisons".

Society recommends beta-interferons and Glatiramer acetate as first line treatments and Natalizumab as second line treatments.[80]

The Swedish MS Society recommends that beta-interferons or Glatiramer acetate should be initiated in patients diagnosed with RRMS according to the 2010 revised McDonald criteria, or if there is suspected MS onset where the MRI shows at least two T2 lesions that are at least 3 millimetres in size.[81]

The Swedish MS Society recommends Fingolimod be used in adults with highly active relapsing MS who fulfils one of the following criteria:[82]

- Treated with a beta-interferon for at least one year and suffered at least one attack in the previous year of treatment and at least 9 T2 hyperintense lesions or at least one gadolinium lesion
- Treatment-naïve with rapidly evolving, severe RRMS with a least two disabling relapses in the last year and at least one gadolinium lesion or a significant increase in T2 hyperintense lesions

The Swedish MS Society makes the same recommendations for Natalizumab as it did for Fingolimod, with the additional recommendation that patients who tested negative for the JC virus should be offered Natalizumab as a first-line treatment after their first relapse if the MRI suggests the patient has highly active MS.[83]

The Swedish MS Society does not provide a DMD stopping criteria. They do not recommend DMD among patients with progressive MS whose EDSS is 7.0 or above, or patients with a slow progression rate without a relapse (one EDSS increase over two years or more).[84]

Regional variations within a country

In addition to national guidelines on clinical management of MS, there could also be regional variations which effect access to DMDs. Examples of this are Spain and Italy, where the regions have high autonomy in outlining clinical guidelines and organization regional/hospital formularies. For example, depending on the region, some MS centres may be able to prescribe all of the nationally-reimbursed DMDs as the first line treatment, while in other regions only certain DMDs can be used first line. As a result, regional formularies dictate treatment which could vary access significantly within a country.

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[80]   Neuro (2010), "Care and treatment", available at http://www.neuroforbundet.se/diagnoser/multipel-skleros-ms/neuroguiden/vard-och-behandling-neuroguiden/, accessed January 3, 2014.

[81]   Swedish MS Society (2013), "Recommendations for treatment with interferon and glatiramer acetate in MS", available at http://www.mssallskapet.se/Lakemedel.html, accessed January 6, 2014.

[82]   Swedish MS Society (2012), "Recommendations for treatment with Gilenya (fingolimod) in MS", available at http://www.mssallskapet.se/Lakemedel.html, accessed January 6, 2014.

[83]   Swedish MS Society (2012), "Recommendations for treatment with Tysabri (natalizumab) in MS", available at http://www.mssallskapet.se/Lakemedel.html, accessed January 6, 2014.

[84]   Swedish MS Society (2012), "Recommendations for treatment of progressive MS", available at http://www.mssallskapet.se/Lakemedel.html, accessed January 6, 2014.

3.2.   The process for assessing innovative treatment

Kobelt et al. suggest that the extremely low usage of some DMDs within some Western European countries are neither explained by price nor by economic conditions but by restrictive reimbursement conditions and patient eligibility conditions to access certain types of treatment.[85] To investigate whether this remains a significant factor in 2013 we looked at reimbursement and HTA recommendations.

3.2.1. Reimbursement

Using a combination of sources, including IMS, literature, and interviews with MS societies and stakeholders, we gathered data on which new treatments are reimbursed by the healthcare system in the different markets and summarised this in Figure 9. All markets provide access to all interferons and Glatiramer acetate (with the exception of Austria which doesn't provide access to Extavia). However, as already discussed in section 2.1.3, "second line" innovative treatments are not available in all countries.

Figure 9: Reimbursement of innovative and established medicines in selected markets
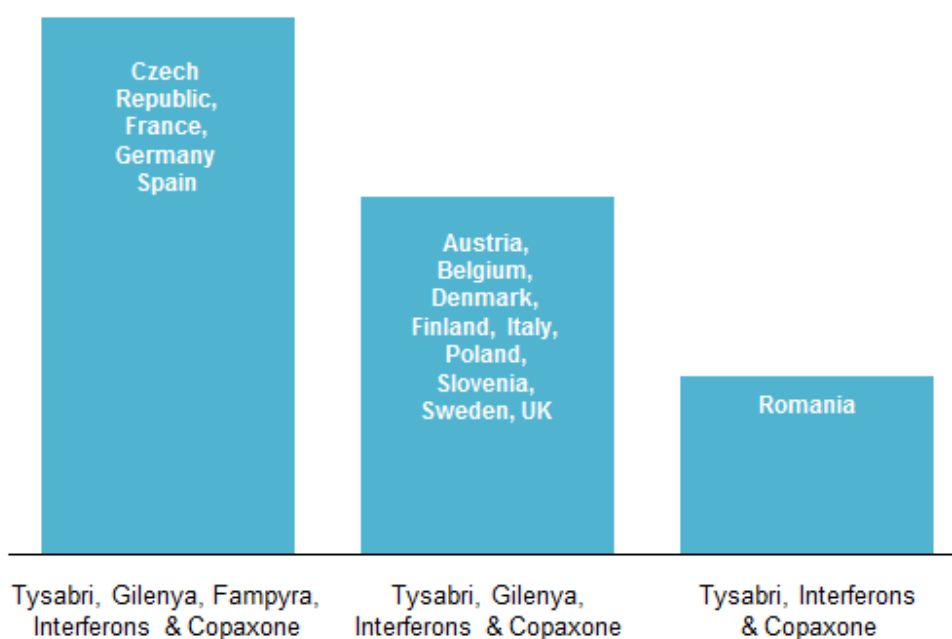
*Source: CRA analysis using multiple sources * Extavia not available in Austria*

However, in addition to rejecting innovative medicines, the reimbursement authorities can impose restriction on their use. Of the selected countries, only Romania, the Czech Republic, and Poland formally limit the number of people with MS eligible to receive DMDs. Additionally, only Poland limits the duration of DMD treatment due to funding restrictions or reimbursement policies, i.e. DMD treatment duration is limited for reasons other than medical

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85   Kobelt and Kasteng (2009), "Access to innovative treatments in multiple sclerosis in Europe", a report prepared for the European Federation of Pharmaceutical Industry Associations (EFPIA).

reasons.[86] These reimbursement restrictions could be another factor contributing to these countries being amongst the three countries with the lowest access to MS DMDs – Poland at the bottom with 13%, and Romania and Czech Republic at 39%.

- In Romania, reimbursement for treatment to patients eligible for state-funded treatment is approved on a case-by-case basis according to whether funds are available. In 2013, 2,300 MS patients received state-funded DMDs.[87] Every two years the number of people receiving treatment is increased and approximately 200 new patients are approved to receive subsidised treatment each year.[88] However, the number of places on the treatment programme remains at the discretion of the health authorities and insufficient numbers of place on the treatment programme has generated a waiting list of about 600 people.[89]

- In the Czech Republic, there has been no budget increase for hospitals for pharmaceuticals since 2010, resulting in a high number of untreated patients in the Czech Republic. Treatment waiting lists were also put in place in 2011.[90]

- In Poland, patients can be treated with a DMD for a maximum of five years.[91] After five years, the treatment "spot" is transferred to the next person on the treatment waiting list.[92]

It seems reasonable to conclude that this is a relevant factor in explaining the lack of access in CEE markets.

3.2.2. Health Technology Assessment

Health Technology Assessments by HTA agencies support decision-making in healthcare at all levels and in many countries serve to educate reimbursement decisions which make DMDs available largely free of charge to patients. In the 2009 Kobelt report, it was suggested the extremely low usage of DMDs in the United Kingdom was a consequence of a restrictive NICE guidance[93]. We examine in table 9 the HTA decisions for Tysabri (Natalizumab) and compare how the resulting national reimbursement guidelines differ across countries. According to the European Medicine Agency label, Natalizumab is recommended for patients

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86   EMSP (2013), "MS Barometer 2013".

87   Nine O'Clock (2013), "6000 to 8000 Romanians diagnosed with multiple sclerosis", available at http://www.nineoclock.ro/6000-to-8000-romanians-diagnosed-with-multiple-sclerosis/, accessed January 7, 2014.

88   Daily News (2013), "Thousands of Romanians with multiple sclerosis will not get treatment unless funding is increased", available at http://www.romania-insider.com/thousands-of-romanians-with-multiple-sclerosis-will-not-get-treatment-unless-funding-is-increased/107980/, accessed January 7, 2014.

89   Romanian MS Society based on doctors coordinators treatment programme

90   Pospiskova, "Multiple sclerosis in Czech Republic".

91   Decree of Ministrer of Health from December 23rd, 2013 DZ. URZ. Min. Zdr. 2013.52 z dnia 23 grudnia 2013 r. , poz. 52. Appendix B.29: Treatment of multiple sclerosis (ICD-10 G 35)..

92   MS Ireland (2013), "Emma Talks at Polish MS Society event", available at http://www.ms-society.ie/blog-articles/1357-emma-invited-to-polish-ms-society, accessed January 7, 2014.

93   Kobelt and Kasteng (2009), "Access to innovative treatments in multiple sclerosis in Europe", a report prepared for the European Federation of Pharmaceutical Industry Associations (EFPIA).

who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon,[94] (patient group 1), as well as patients with rapidly evolving severe relapsing remitting multiple sclerosis[95] (patient group 2). However, in a number of countries the HTA process has restricted the use of the medicine.

Table 9: Health Technology Assessment of Tysabri (Natalizumab) in selected European countries

Country (body)	Decision	Recommendation and patient eligibility
England (NICE)	Favourable but restricted to patient group 2.	Natalizumab is recommended as a possible treatment but only for people with rapidly evolving severe relapsing-remitting multiple sclerosis
Netherlands (CVZ)	Favorable but restricted to patient group 1	Natalizumab is offered as a possible treatment only for people who fail to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon.
France (HAS)	Fully reimbursed for both patient group 1 & 2	Natalizumab provides a moderate improvement in actual benefit (Level III) as monotherapy for the primary treatment of aggressive forms of relapsing-remitting MS.
German (IQWiG)	Fully reimbursed for both patient group 1 & 2	Natalizumab is reimbursed according to EMA label indication
Italy (AIFA)	Favourable but reimbursement narrower than label description	Restriction in patient group 1: at least 2 relapses in the last year, or 1 relapse with residual disability (2 or more at EDSS); group 2 the same
Belgium (RIZIV/INAMI)	Reimbursed for both patient group 1 & 2 but with variations to EMA label	Use of Natalizumab is further restricted to patients with EDSS under or equal to 6.5
Czech Republic	Favourable but reimbursed for both patient group 1 & 2, with variations	Some further restriction in patient group 1: at least 2 relapses within 1 year, or 3 relapses within 2 years; group 2 the same

Source: CRA analysis

In most countries, including Germany, France, Spain, Portugal, Denmark, Ireland, Sweden, Finland, Norway, Slovenia, Switzerland, and Greece, HTA bodies have recommended that

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94   at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in MRI or at least 1 Gadolinium-enhancing lesion . A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

95   RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

Natalizumab be fully reimbursed according the full EMA label prescription (i.e. covering both patient group 1 and 2). However, this is not the case in all countries, for example, Italy and the Czech Republic have imposed restrictions on patient group 1. Belgium has further restrictions for patients with EDSS under or equal to 6.5, whilst Hungary has broadened patient group 1 to also include patients who failed under Glatiramer acetate.

Other countries such as Austria, Netherlands, Slovakia have opted for only reimbursing patients who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon (group 1) whilst the UK has opted for only covering patients with rapidly evolving severe relapsing remitting multiple sclerosis (group 2).

In addition to restrictions imposed on the coverage, we also look at the extent to which the HTA and reimbursement process can have also an impact on the time patients must wait to have access to the treatment. Using IMS data, we undertook an analysis to show the relative delay in access/uptake of two of the main innovative second line treatment line treatments, Fingolimod and Natalizumab. We determined the time of availability as the point when significant uptake began (the month at which unit sales as a percentage of the latest month, increased over the previous month by several percent). Although there was no IMS data available for the UK, the data was available publically. As illustrated in Figure 10 (Natalizumab) and Figure 11 (Fingolimod), despite similar HTA assessments, there is still important variation in the product entry/uptake with some countries exhibiting a significant delay.

Figure 10: Tysabri (Natalizumab) market entry based on IMS data
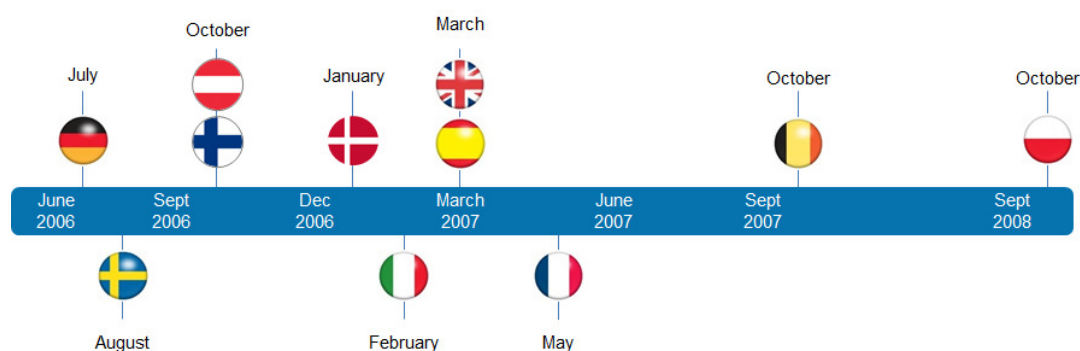
Source: CRA analysis using IMS and MS society (UK)

Figure 11: Gilenya (Fingolimod) market entry based on IMS data
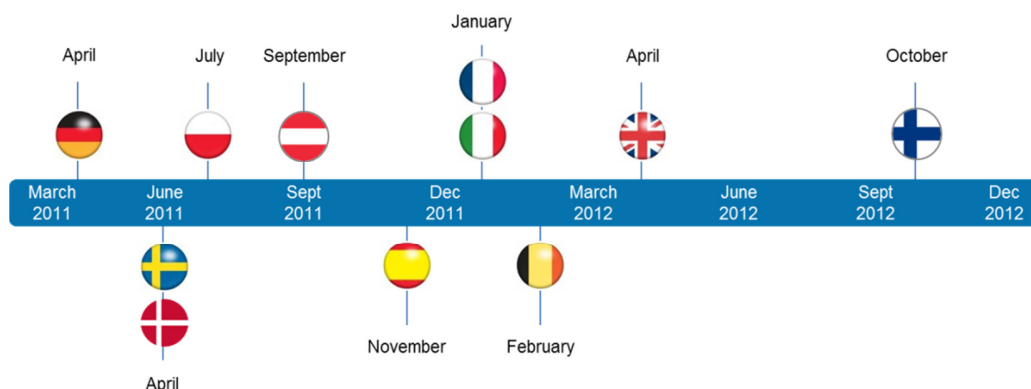
Source: CRA analysis using IMS and MS society (UK)

Whilst some countries such as Germany, Sweden, Austria and Denmark are systematically among the first countries to gain access to innovative medicines, other countries vary in their approval timeline. In the case of Fingolimod, Poland was much quicker to allow market entry than for Natalizumab, whilst Finland and the UK were significantly slower compared to the entry of Natalizumab. In the UK, the NICE appraisal initially rejected Fingolimod and only once there was a patient access scheme was this ultimately recommended and the product was made available to patients.[96]

3.3. Affordability

Another explanatory factor is the price of medicines. We would expect that countries with higher income pay higher prices, but access could depend on the affordability of medicines (and associated medical costs).

To determine prices for all MS products on the market, we have used published prices to estimate ex-factory prices. These were in some cases publically available prices published on the local authorities' webpages (e.g. UK). If the ex-factory price was not available, but the pharmacy or public price was, we used an estimated price based on average industry margins (e.g. Spain), or calculated price based on fixed and controlled industry margins (e.g. Italy). These are illustrated in Figure 12 below. As with any analysis of prices, this is based on list prices and does not include confidential rebates and discounts.

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[96]   The draft recommendation was published in August 2011. After Novartis submitted a proposed PAS, NICE still did not recommend it in the second draft recommendation, published in December 2011. Novartis revised its analyses for a subgroup of the licensed population, so Fingolimod is now recommended for this subgroup, i.e. "adults with highly active RRMS, whose relapses have increased for stayed the same compared to the previous year, despite them taking beta interferons". See the NICE 2012 Fingolimod commentary for details around the recommendation history.

Figure 12: Price comparison across countries (Germany=100)
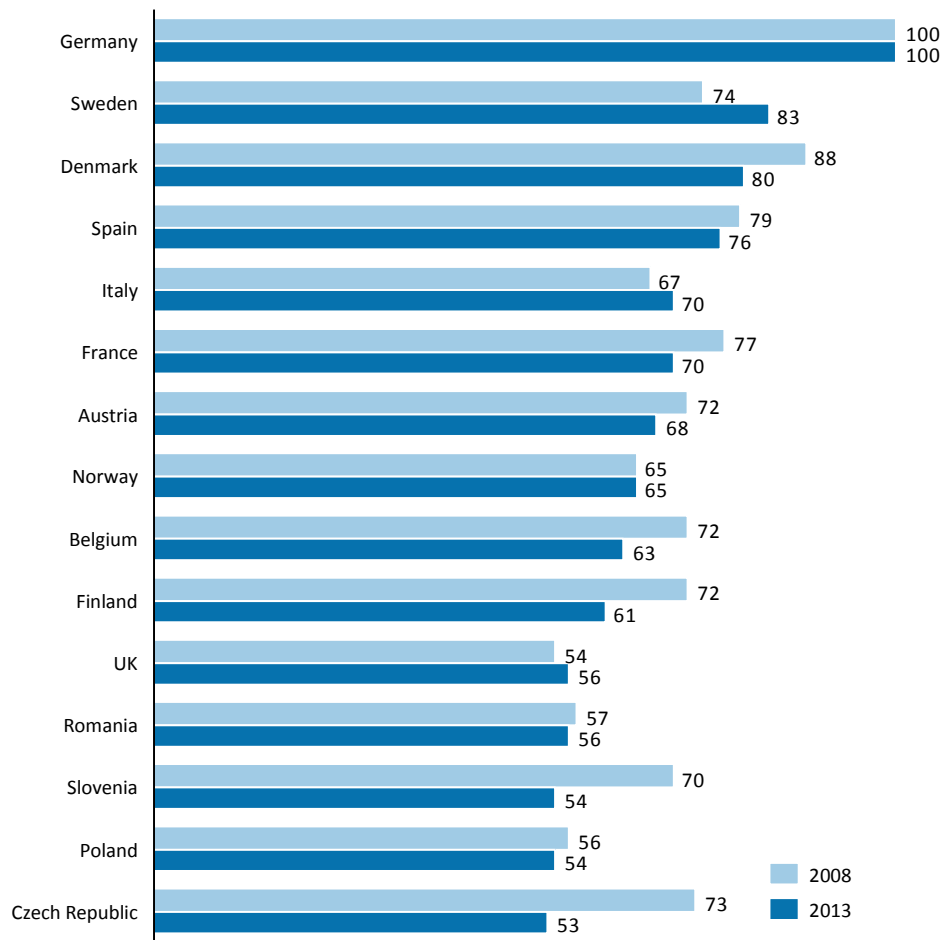
Source: CRA analysis using IMS data, local drug price databases; Note: Weighted manufacturer prices

It is interesting to compare prices to health expenditure (a proxy for income). We created an index using the level of prices and expenditure in Germany as the base. Following Kobelt we determined the price index using the weighted average price for each drug for each country and divided this by Germany's price. We calculated the relative health expenditure per capita number using OECD data (as with Kobelt dividing each country's health expenditure per capita by Germany's).

We would expect countries with higher expenditure to pay higher prices. Figure 13 shows the price index of the selected countries as a function of relative HE/capita. The line of best fit is determined using the Western European countries (blue). The figure shows that apart from Slovenia, the CEE countries (red) have a higher price index to relative HE/capita ratio relative to the Western European countries which could be a further factor influencing access.

Figure 13: Correlation between relative price index and relative health expenditure per capita in 2013
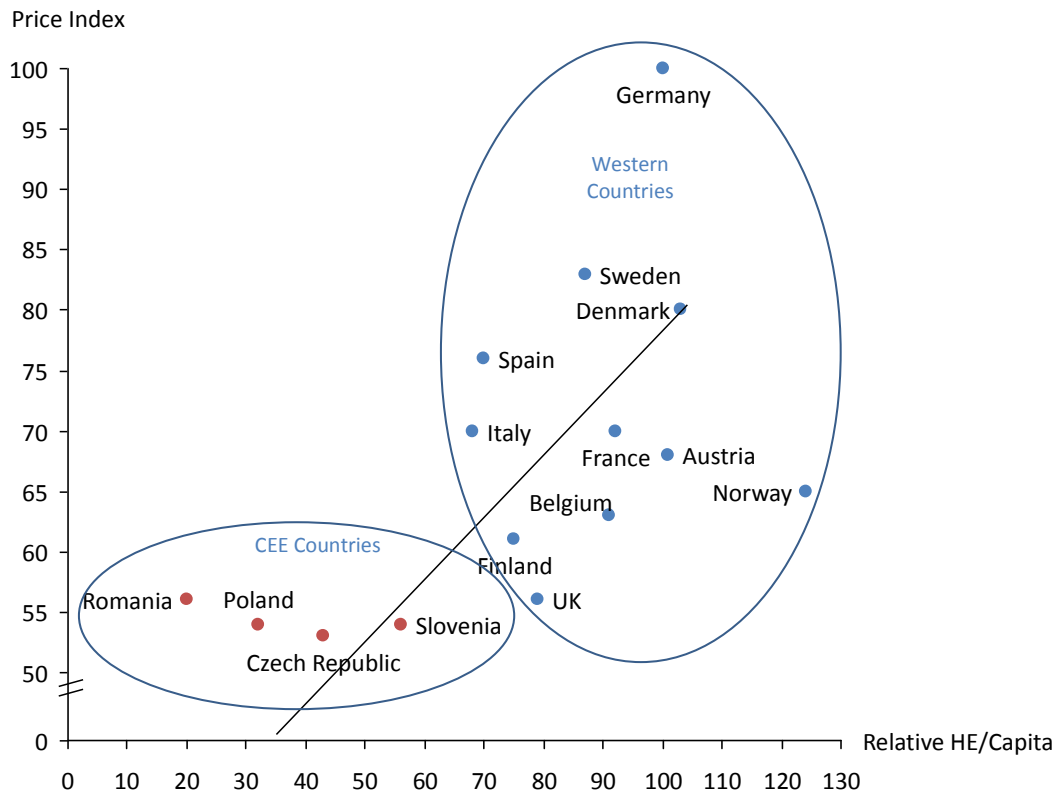
Source: CRA Analysis

This suggests that prices relative to income remain higher in CEE markets.

Another way to examine this is to create an 'affordability index' as created by Kobelt. This is calculated by combining the relative price of medicines paid by each country with the total level of healthcare expenditures into one index. This enables us to compare each country's relative ability to afford DMD with the context of their healthcare budget, using Germany as a benchmark of 100. The affordability index shows to what extent DMDs can be taken up within the health care budget at the given price. A higher index means that it is more difficult for the country to afford innovative medicines.

Table 10: Comparison of prices, health expenditures and ability to afford

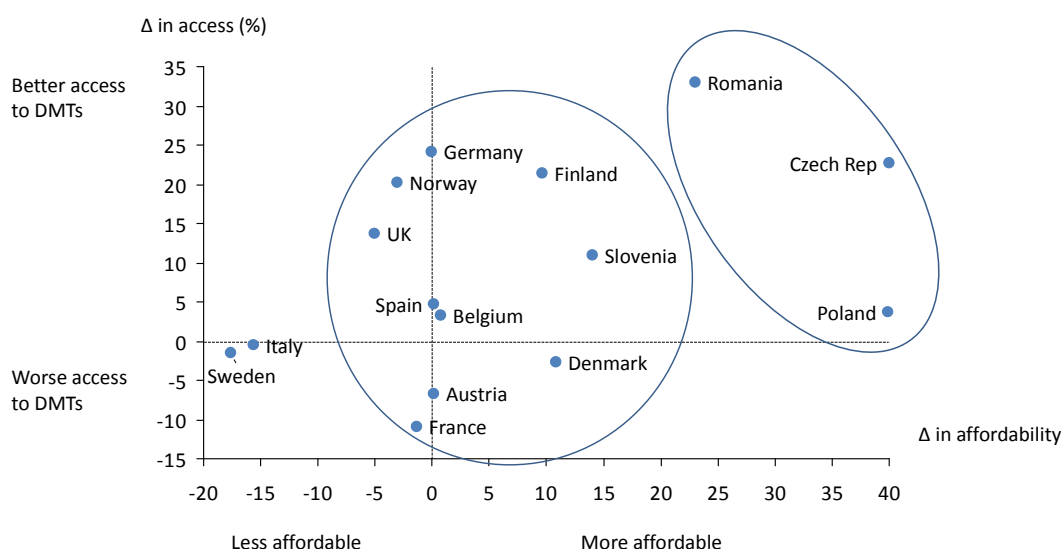| Country	Price index Germany = 100	Relative HE/capita Germany = 100	Affordability index Germany = 100
Austria	68	101	67
Belgium	63	91	69
Czech Republic	53	43	123
Denmark	80	103	77
Finland	61	75	81
France	70	92	76
Germany	100	100	100
Italy	70	68	103
Norway	65	124	52
Poland	54	32	168
Romania	56	20	275
Slovenia	54	56	96
Spain	76	70	109
Sweden	83	87	96
UK	56	79	71

CRA analysis using IMS data, local drug price databases, and OECD 2011 HE/Capita data

Figure 14: Affordability Index (Germany = 100)
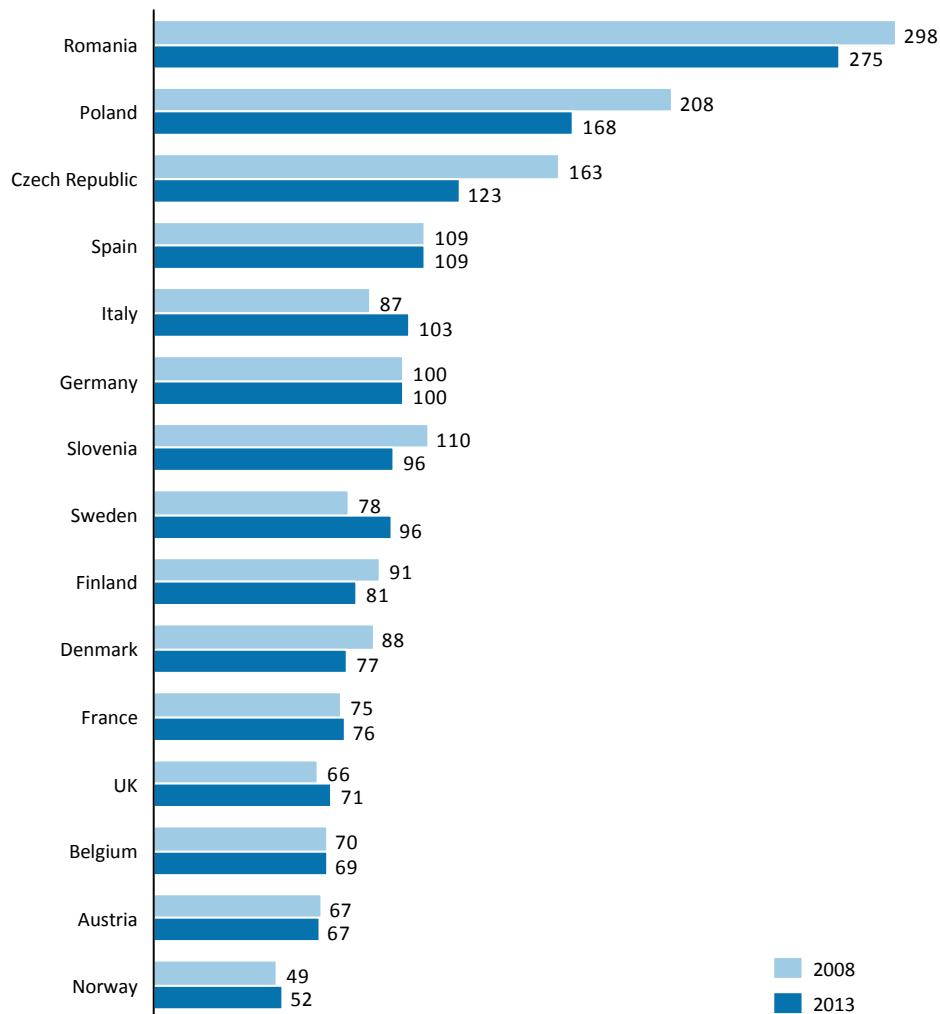
CRA analysis using IMS data, local drug price databases, and OECD 2011 HE/Capita data

Figure 15 illustrates the change in the selected countries affordability level between 2008 and 2013. The affordability index has exhibited a decrease in all Eastern European countries as well as in some Northern European countries (Finland and Denmark) meaning that treatment has become more affordable in these countries. However, other countries such as Italy, Sweden and the UK have seen an increase in their index figure, meaning that treatment have become relatively less affordable than they used to be. This is most likely due to increases in uptake of new innovative medicines used as second line treatment as shown in section 2.1.3 are relatively more expensive. DMD have become relatively more affordable in new member states largely due to an increase in healthcare spending combined with a decrease in the relative price of DMDs. This has been associated with an increase in access to DMDs in these countries.

Figure 15: Impact of change in affordability on access

3.4.   Patient Registries/Databases

The data and information on MS gathered as part of this report clearly indicates that no one country provides adequate level of data or information on MS and that the availability of data varies widely both within region and between countries.

A number of countries in Europe have developed patient registries. The objective is to improve the knowledge and management of MS, and as a tool for raising awareness of MS among both clinicians and the general public. These patient registries have helped to collect secondary data related to patients with a specific conditions and play an important role in improving the management of care, as well facilitating post marketing surveillance. Table 11 provides an overview of existing national registries that have been developed in Europe.

Table 11 Overview of National MS registries in Europe

Registry	Start	No of Centres	Coverage
Danish MS registry	1998	22	90-95%
Swedish MS Registry	1997	27	50%
Norwegian MS registry	1998	-	50-60%
Italian MS Database Network	2001	26	
German MS Registry	2002	86	93.5%
European Register for Multiple Sclerosis (EUReMS)	2012	-	-

Source: Flachenecker, P. (2008).

3.5.   Summary

Kobelt et al conclude that the major differences in uptake of DMDs for MS in Europe can be observed between new and old member states, are largely due to differences in wealth, especially in Central and Eastern European countries where access is found to be less than half that of Western European countries, despite lower prices in most the new EU member states. However, within Western Europe, differences in access are explained by restrictive reimbursement decisions as well as by a clear lack of neurologists in some countries. Our results are largely consistent with these findings. We find that:

- There is a correlation between the level of access and the healthcare infrastructure (as proxied by the number of neurologists);

- Although there are differences in clinical guidelines, these do not seem to explain much of the variation, however, there are some countries (such as the Czech Republic) with low access and restrictive guidelines where this appears an important barrier to access;

- In terms of reimbursement and HTA decisions, despite similar HTA assessments, a number of countries have restricted the use of the medicines by reimbursing only certain patients who meet strict eligibility criteria. There are also still some important variations in the product entry/uptake with some countries exhibiting a significant delay. Whilst some countries such as Germany, Sweden, Finland, Austria and Denmark are systematically among the first countries to gain access to innovative medicines, other countries vary in their approval timeline with significant reimbursement barriers remaining in CEE market affecting access in these markets.

- In terms of affordability, we do find a relationship between affordability and improved access. DMD have become relatively more affordable in new member states largely due to an increase in healthcare spending combined with a decrease in the relative price of DMDs. This has been associated with an increase in access to DMDs in these countries but the affordability remains a barrier to access for these countries;

- MS registries have been developed in some European member states. They provide a key tool in managing diseases and have become useful for studying disease characteristics in large populations and monitoring the long-term outcome of disease-modifying therapies. This helps provide information on the provision of treatments, services and supplies within a given area.

4.   Policy implications

In the previous chapters we have reviewed how access to MS medicines varies across European member states and the factors that help to explain these differences. It is clear that patient access to MS treatments has significantly increased over the last five years even though prevalence has increased. However, as can be observed in section 4.2, there remains substantial variation both across and within countries. In this chapter, we consider the policy implications of the variation in access to MS treatment.

4.1.   Healthcare provision devoted to MS

Unsurprisingly, there is a relationship between access to medicines and the investment in diagnosis and treatment of MS. Although, it is not possible to directly compare the spend on MS treatment in different European member states, we can look at proxies such as the number of specific healthcare professionals, e.g. neurologists, who are typically responsible for diagnosis and treatment, and nurses. Given the increasing prevalence of MS, countries with low levels of access need to consider devoting more resources to MS, for example by increasing the number of neurologists and MS nurses.

4.2.   National strategy and aim to reduce regional variation

As discussed in the previous chapters, there is considerable variation in access to MS treatment across European member states; however, to a degree this masks the level of variation within the member states. As shown in the figure below, there is often even more variation within regions of the same country. Even if we consider a country such as Sweden, where access is transparent and has been tracked over time, significant variation continues to persist (see Figure 16). A similar situation can be found in low access country, for example, in the UK, where access varies from 30% in Wales to 68% in Northern Ireland.[97]

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[97]   "A lottery of treatment and care – MS services across the UK"

Figure 16: Estimated percentage of patients with relapse-remitting multiple sclerosis who were being treated with DMDs, 2012
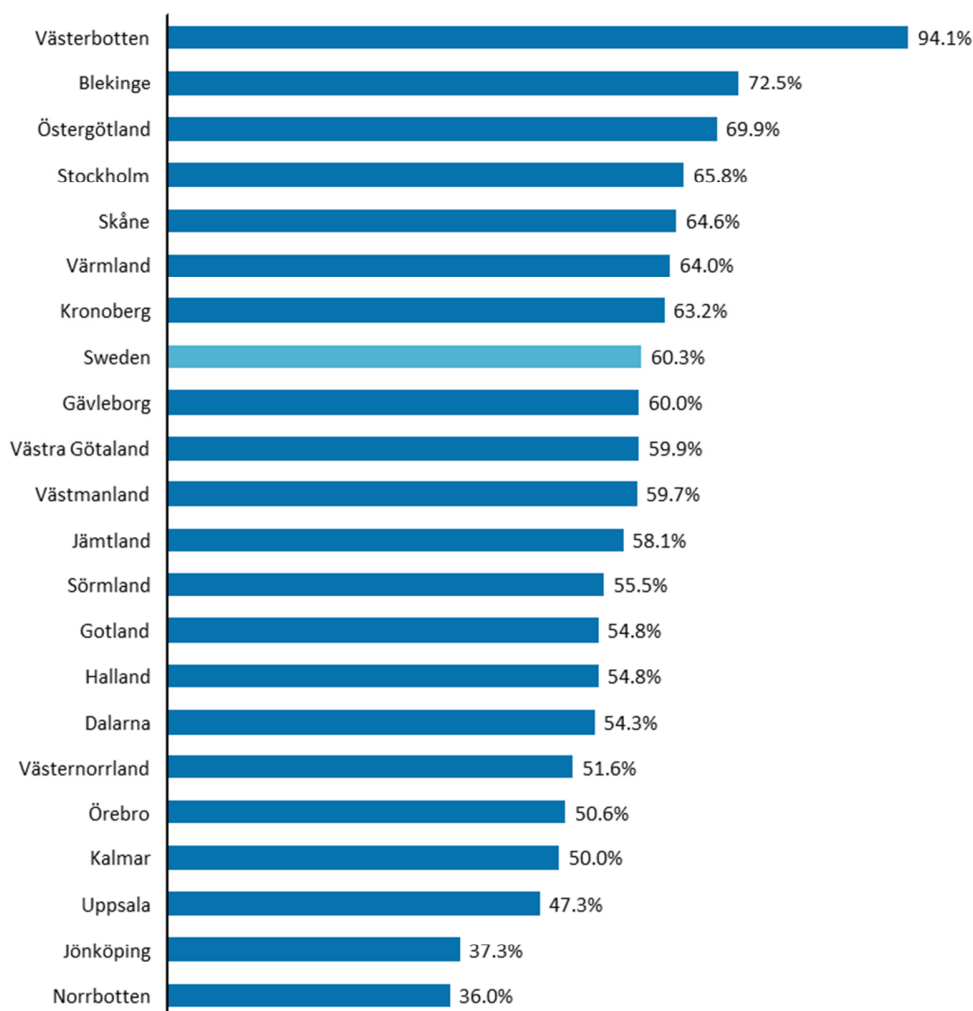
Reducing variations in access within a country has a number of implications for policy:

- The need for a national strategy. For example, in the UK there have been calls for a neurology 'tsar'. The UK Government's own audit office supports the creation of a targeted national strategy for neurological conditions. The aim is that a national strategy will assist in addressing the variations in service provision for people with MS. [98]

- A requirement by local payers to follow the national strategy: the local reimbursement decision needs to be consistent with national policy. It is unsurprising

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[98]   "Access to treatments and services for people with MS in the UK" Advances in Clinical Neuroscience and rehabilitation, Supplement to ACNR Volume 12 Issue 2 MAY/JUNE 2012 ISSN 1473-9348

that variation in access is seen as particularly problematic in the UK and Sweden which have a decentralised system of healthcare decision making.

- Sustained and focused strategy: Policies to be applied consistently within a country over a long period of time. For example, the Swedish healthcare system recognised 10 years ago that many RRMS patients were not being treated, whereas a large number of SPMS patients were being treated despite the lack of evidence of treatment benefits. Over the last decade, the Swedish healthcare system successfully reversed this treatment trend such that 60.3% of RRMS and 7.4% of SPMS patients are treated. However, there is still a wide range in terms of treatment rate within Sweden (see Figure 16).[99] The continued significant differences between the Swedish counties demonstrate the need for policies to be applied more consistently within a country.

- However, a clear policy can increase access rapidly: The Czech Republic has exhibited a significant increase in access between 2013 and the 2008. This is due, to a large extent, to a legislative decree (2009) which states that all eligible patients diagnosed with MS have the right to be treated within four weeks of diagnosis with a DMD.[100]

4.3.   Application of clinical guidelines

Although there has been considerable academic effort in developing criteria for diagnosing MS, there remains considerable variation in how they are used. The McDonald criterion has provided a uniform approach but has not been universally accepted.[101] This has again been identified as an issue in a number of countries including the UK. It is argued that given there are European guidance for standard treatments and therapies - such as the European Code of Good Practice – these need to be more consistently applied. There are a number of legitimate concerns regarding the use of guidelines today:

- Guidelines should be updated: Given the changes in the treatment for MS over the last ten years and the number of new products that are coming to market, it is important that clinical guidelines are kept up to date. Updates should incorporate recommendations around the controversial aspects of care, for example how early

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[99]   "Quality and Efficiency in Swedish Health Care Regional Comparisons 2012"

[100]   Discussion with local stakeholder

[101]   The major advantage of the McDonald criteria over previous diagnostic criteria is that MRI can help to establish a fundamental pattern of MS lesion development (DIS and DIT) in the absence of clinical symptoms or signs, allowing an earlier diagnosis of MS with high accuracy.

treatment should be initiated, as consensus is reached so that they are communicated to all audiences.[102]

- Guidelines should be adhered to: Even where guidelines are clearly set out and kept up to date, they are not necessary adhered to. For example, the 18 week target recommended by NICE from GP referral to diagnostic tests to treatment was not achieved by 13% of MS centres in the UK.[103] In terms of diagnosis, the median time between initial referral and final diagnosis of patients was more than the NICE standard of 12 weeks, according to the 2011 UK national audit.[104] Adherence to guidelines, especially if they are national guidelines, ensures uniform treatment methods.

- Goals of guidelines should be clear: This does not mean every MS patient should be on DMDs, but rather that an assessment is made regarding the appropriate level of coverage to aim for. For example, the Swedish MS Association (SMSS) issues recommendations for the use of immunomodulatory therapy. They estimate that approximately 75% of patients with RRMS should be treated while only a small percentage of SPMS patients should be treated.[105] Targets are useful to prompt change towards the ideal.

4.4.   Collecting patient data through registries/databases

Publically available MS registries/databases need to be developed in order to provide sufficiently detailed information on the provision of treatments, services and supplies within a given area that may be used to compare different levels of health care within and between these regions.[106]

In the long-term, MS registries will also serve to monitor the health care situation of MS patients over time. This includes the implementation of guidelines relating to care and treatment, measure the improvements that have taken place, and reveal shortages and/or misalignment in health care services. This will ensure the long-term follow-up of the individual

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102   For example, there is a debate on when treatment should be initiated for MS given the need to balance the budget with the difficulty in an early definite diagnosis of MS with the increasing evidence that there are benefits to early treatment as it slows progression of MS and in turn reduces the degree of irreversible tissue injury and degeneration of the nervous system. See, for example, "When to Initiate Disease-Modifying Drugs for Relapsing RemittingMultiple Sclerosis in Adults?" Mona Alkhawajah and Joel Oger, Multiple Sclerosis International Volume 2011, Article ID 724871, 11 pages doi:10.1155/2011/724871; Coles AJ, Cox A, Le Page E, et al., The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy, J Neurol, 2006;253(1):98–108; "Disease Modifying Drugs for MS improve Quality of Life and reduce disease progression" Advances in Clinical Neuroscience and rehabilitation, Supplement to ACNR Volume 12 Issue 2 MAY/JUNE 2012 ISSN 1473-9348.

103   MS Society UK (2011), "MS 2015 vision: a report by the MS Forum

104   Access to treatments and services for people with MS in the UK" Advances in Clinical Neuroscience and rehabilitation, Supplement to ACNR Volume 12 Issue 2 MAY/JUNE 2012 ISSN 1473-9348

105   "Quality and Efficiency in Swedish Health Care Regional Comparisons 2012"

106   Flachenecker, P. (2008). National MS registries. Journal of neurology, 255(6), 102-108.

patient by increasing the understanding and knowledge about MS and allowing healthcare system to make informed decisions about MS.[107]

4.5.   Optimising the assessment and approval process

It is important to recognise that across Europe healthcare budgets are under unprecedented pressure but when new treatments are launched on the market, the administrative process for assessing the medicines should be as efficient as possible. We have shown in the last chapter how the HTA process can explain the delay in medicines being used by patients in some countries.

However, the HTA process should be used to assess the value of medicines rather than as a cost containment device. There are also discussions as to whether HTA should include a full assessment of societal value. In some countries, there is clearly a process for systematically allowing for these. In other systems, some effort has been made to allow the societal perspective to be taken into account in some way but this appears to have considerably less impact on decision-making than evidence on health benefits and costs to the healthcare system. For treatments where quality of life is a significant factor, long-term benefits are difficult to measure, but the impact on extended families and carers is significant, and the ability of the patient to work is highly likely to be affected.[108] MS is often diagnosed when patients are in their twenties and thirties and therefore can have a significant impact on employment and their ability to contribute to the economy. In addition, MS affects more women than men and is most frequently diagnosed in women in their childbearing years[109], at a time when they may be thinking about starting a family. Moreover, productivity losses due to disability in MS represent 37% of total MS costs to society while DMD treatments represent 12% of total MS costs to the society.[110]

HTA therefore needs to be applied with considerable care to MS products so that MS patients are not penalised. Mechanisms such as managed entry schemes and coverage with evidence development may be appropriate for particular products to ensure that patient access occurs on a timely basis.

4.6.   Improving affordability and removing administrative barriers

As we have set out in the previous chapter there is a relationship between access and affordability. Policies that improve affordability should be considered.

Some policies prevent prices from reflecting the level of income of each market, such as inappropriate international price benchmarking where high income countries adjust their prices towards those in low income countries. These practices as well as the promotion of

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[107]   Ibid

[108]   Most people are diagnosed between the ages of 20 and 40, and for half of them unemployment follows, on average three years after. "MS Barometer 2013 Widespread health inequalities revealed"

[109]   Confavreux, C., Hutchinson, M., Hours, M. M., Cortinovis-Tourniaire, P., & Moreau, T. (1998). Rate of pregnancy-related relapse in multiple sclerosis. New England Journal of Medicine, 339(5), 285-291.

[110]   European Journal of Health Economics: "Cost and quality of life of with MS in Austria"", 2006

product re-exportation into high income countries which contribute to shortages in low income countries should be reconsidered to improve affordability and patient access.[111]

To the extent these can be used to manage affordability, they should allow removal of arbitrary administrative barriers:

- Arbitrary limits on number of patients: This is a mechanism aimed at managing the budget but means that some patients eligible for treatment may not have access to treatment, e.g. in Romania, the Czech Republic, and Poland. In Romania, urgent cases are fast tracked, which raises the question of how a case should be prioritized, i.e. whether it should be based on the patient's economic potential, the patient's quality of life, or delaying the onset of more severe forms of MS. Additionally, the waiting list prevents patients getting early access and may therefore result in the disease progressing to a point where the treatment is of less clinical value, further exacerbating the disease and access issue;

- Limited duration of treatment: Due to budget constraints, countries may limit public reimbursement of DMDs to a given number of years, for example in Poland where public reimbursement of a DMD is limited to 5 years. Given the individualised progression of the disease, value of adherence, and continuity of care, this is likely to be particularly detrimental to the patient's disease and quality of life;

Improving affordability of MS medicines could lead to the removal of these arbitrary rationing devices allowing greater access to patients on the basis of clinical judgement and bring significant benefits to the health system and even the economy.

4.7.   Summary

In summary, the analysis in the preceding chapters has set out the large variation in access to MS treatments and the range of explanatory factors. In order to reduce the variation in access there are a number of policy proposals:

- In some markets, this requires greater investment in Healthcare infrastructure devoted to MS;

- A national strategy is an important building block, that provides consistency over time and sets clear targets;

- Publically available MS registries/databases need to be developed in order to measure the prevalence of MS country by country, to standardise methodology across countries and to assess, compare and enhance the status of people with MS across Europe.

- It is important that clinical guidelines are kept up to date but more importantly that they are actually used in practice;

- Affordability is a key barrier to access for MS products. Some policies prevent prices from reflecting the level of income of each market, such as inappropriate international

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[111] CRA International (2012); The implications of international reference pricing and parallel trade on social welfare and patient access, a report for EFPIA, Project No. D18046-00

price benchmarking, where high income countries adjust their prices towards those in low income countries. These practices as well as the promotion of product re-exportation into high income countries, which contribute to shortages in low income countries, should be reconsidered to improve affordability and patient access.

- To the extent that affordability can be improved, this would allow the removal of arbitrary administrative processes that are being used to manage budgets allowing greater access to patients on the basis of clinical judgement and bring significant benefits to the health system and even the economy.